Biomedicine & Pharmacotherapy 134 (2021) 111172

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

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

Review

Role of non-coding RNAs in modulating the response of cancer cells to paclitaxel treatment

Soudeh Ghafouri-Fard [a], Hamed Shoorei [b], Atefe Abak [c], Sayed Haidar Abbas Raza [d], Martin Pichler [e,f,**], Mohammad Taheri [g,*]

[a] Urogenital Stem Cell Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[b] Department of Anatomical Sciences, Faculty of Medicine, Birjand University of Medical Sciences, Birjand, Iran
[c] Department of Medical Genetics, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[d] College of Animal Science and Technology, Northwest A&F University, Yangling, Xianyang, China
[e] Research Unit of Non-Coding RNAs and Genome Editing in Cancer, Division of Clinical Oncology, Department of Internal Medicine, Comprehensive Cancer Center Graz, Medical University of Graz, 8036 Graz, Austria
[f] Department of Experimental Therapeutics, the University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
[g] Urology and Nephrology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Keywords:
Paclitaxel
miRNA
lncRNA
Chemotherapy
Cancer

ABSTRACT

Paclitaxel is a chemotherapeutic substance that is administered for treatment of an extensive spectrum of human malignancies. In spite of its potent short-term effects against tumor cells, resistance to paclitaxel occurs in a number of patients precluding its long-term application in these patients. Non-coding RNAs have been shown to influence response of cancer cells to this chemotherapeutic agent *via* different mechanisms. Mechanistically, these transcripts regulate expression of several genes particularly those being involved in the apoptotic processes. Lots of *in vivo* and *in vitro* assays have demonstrated the efficacy of oligonucleotide-mediated microRNAs (miRNA)/ long non-coding RNAs (lncRNA) silencing in enhancement of response of cancer cells to paclitaxel. Therefore, targeted therapies against non-coding RNAs have been suggested as applicable modalities for combatting resistance to this agent. In the present review, we provide a summary of studies which assessed the role of miRNAs and lncRNAs in conferring resistance to paclitaxel.

1. Introduction

Paclitaxel is a chemotherapeutic agent being used in a wide range of human malignancies [1]. This agent has uncommon biochemical properties. Its structure contains a complex diterpene, a taxane ring, a four-membered oxetane ring and an ester side chain at location C-13 [1]. The Food and Drug Administration has approved paclitaxel for the treatment of a variety of cancers including ovarian cancer, breast cancer, lung cancer, and Kaposi's sarcoma [2]. In addition, it is administered off-label for the treatment of several other cancers [2]. Mechanistically, this agent promotes the polymerization of tubulin to stable microtubules, blocking cells in the G2/M stage of the cell cycle and decapitating them from making a normal mitotic apparatus [1]. In vitro studies have shown that this agent decreases the crucial amounts of purified tubulin

Abbreviations: lncRNA, long non-coding RNAs; miRNAs, microRNAs; APC, adenomatous colon polyposis protein; CK- 1, casein kinase-1; 3′UTR, 3′-untranslated region; NSCLC, Non-Small Cell Lung Carcinoma; LC, Lung Cancer; LCSCs, Lung Cancer Stem Cells; OC, Ovarian Cancer; EOC, Epithelial ovarian cancer; CC, Cervical Cancer; EC, Endometrial carcinoma; BCa, Breast Cancer; TNBC, Triple Negative Breast Cancer; MTMECs, Minimally Transformed Mammary Epithelial Breast Cancer Cells; BCSC, Breast Cancer Stem Cells; CRC, Colorectal Cancer; GC, Gastric cancer; HCC, Hepatocellular Carcinoma; PCa, Prostate Cancer; CML, Chronic Myelogenos Leukemia; OS, Osteosarcoma; NPC, Nasopharyngeal carcinoma; BLC, Bladder Cancer; OS, overall survival; DFS, disease-free survival; RFS, relapse-free survival; LAD, Lung Adeno carcinoma; EC, Endometrial Cancer; RCC, Renal Cell Carcinoma; CRISPR, clustered regularly interspaced short palindromic repeats; gRNA or sgRNA, genome-editing strategy includes two components: a guide RNA; Cas protein, CRISPR-associated endonuclease; HGSOC, High-grade serous ovarian cancer; ATC, Anaplastic thyroid carcinoma; RES, recognition of reticuloendothelial system; MTD, maximum tolerated doses; nab, nanoparticle albumin-bound.

* Corresponding author.
** Corresponding author at: Research Unit of Non-Coding RNAs and Genome Editing in Cancer, Division of Clinical Oncology, Department of Internal Medicine, Comprehensive Cancer Center Graz, Medical University of Graz, 8036 Graz, Austria.
E-mail addresses: martin.pichler@medunigraz.at (M. Pichler), mohammad_823@yahoo.com (M. Taheri).

https://doi.org/10.1016/j.biopha.2020.111172
Received 18 November 2020; Received in revised form 12 December 2020; Accepted 15 December 2020
Available online 24 December 2020

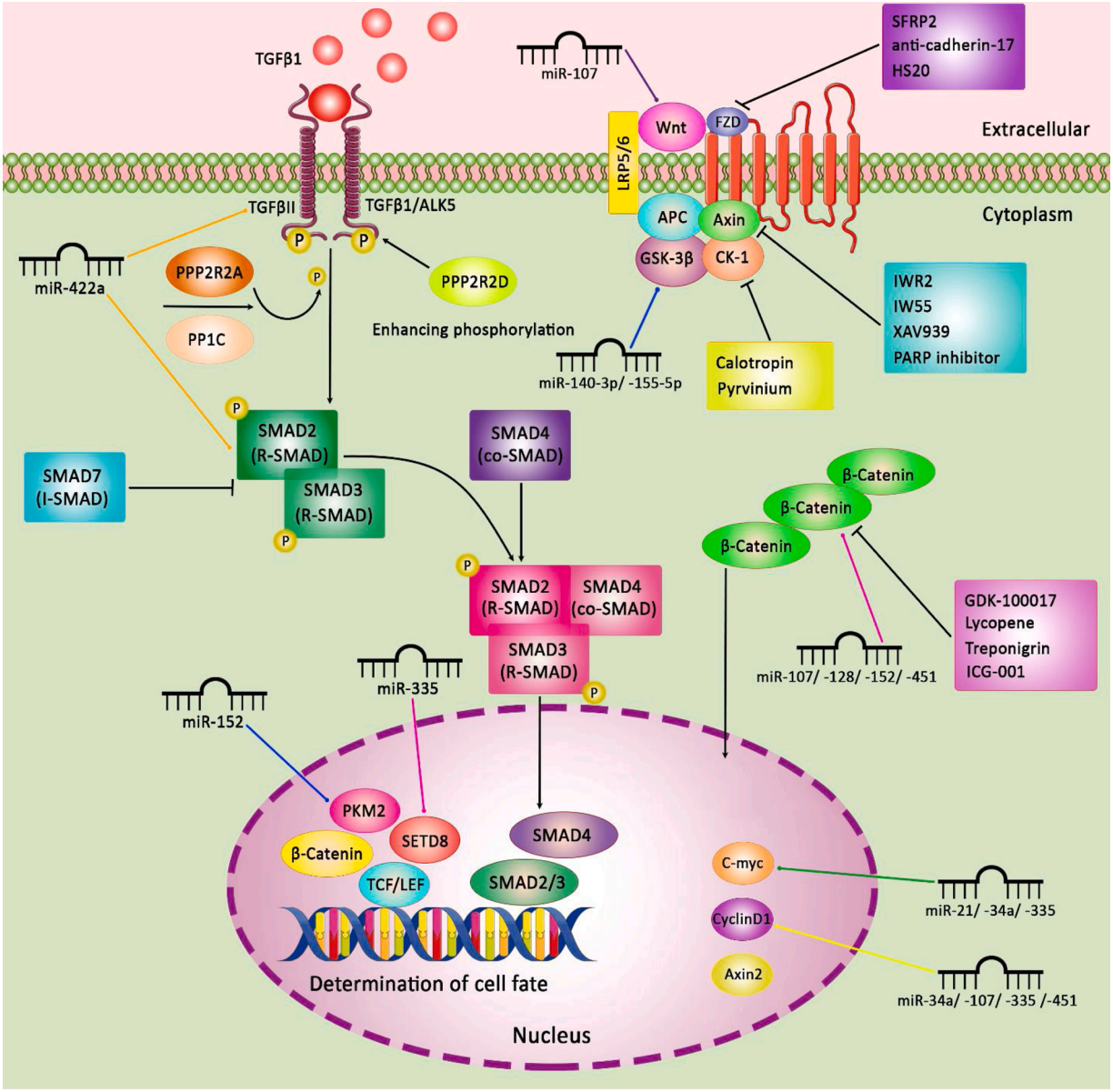

Fig. 1. A schematic representation of the TGF-β, Smad and Wnt/β-catenin signaling pathway causing paclitaxel resistance in cancer cells *via* dysregulation of miRNAs. β-catenin can interact with GSK3β, axin2, APC, and CK-1. Through binding with FZD and LRP5/6 coreceptor complex, Wnt can inhibit β-catenin phosphorylation and its transfer to the nucleus. In nucleus, β-catenin can bind to TCF/LEF transcription factors in order to enhance expression of targets such as cyclin D1, c-myc, or c-jun. Some studies have demonstrtaed the effect of Wnt/β-catenin and TGF-β expression in inducing drug resistance in various human cancer cells. The abnormal expression of miRNAs could negatively regulate Wnt, GSK3β, β-catenin, and TGF-βII which can play a crucial role in chemotherapy resistance especially reducing the effect of paclitaxel in target cancer cells. miR-152 induces activation of PKM2, cell proliferation, and tumorigenesis as well as paclitaxel resistance.

Table 1
Role of miRNAs in the modulation of response of lung cancer to paclitaxel (ANCs: adjacent normal controls).

Cancer type	microRNA& Expression Pattern	Animal	Human	Assessed cell line	Targets/ Regulators	Signaling Pathway	Function	Ref
Non-Small Cell Lung Carcinoma (NSCLC)	miR-935 (Up)	–	30 pairs of NSCLC tissues and ANCs	A549, 293 T	SOX7, Bax, Bcl-2, p-Akt	AKT	Downregulation of miR-935 could enhance paclitaxel sensitivity of NSCLC cells *via* promoting the expression level of SOX7.	[19]
NSCLC	miR-421 (Up)	6-week-old nude mice	10 NSCLC serum samples and 10 non-tumor serum specimens	EAS-2B, CCD19-lu, A549, H358, H1650, H460, H1975	KEAP1	Wnt/ β-catenin, AKT/ERK	Blocking the expression of miR-421 *via* AMO could promote ROS levels and the expression level of KEAP1, and thereby enhancing paclitaxel sensitivity in NSCLC and reducing cell proliferation, invasion, and migration.	[20]
NSCLC	miR-4262 (Up)	5-week-old nude mouse	20 pairs of NSCLC tissues and ANCs	A549, H1299, MRC5, A549/PTX, H1299/PTX	PTEN	PI3 K/AKT	Downregulation of miR-4262 *via* modulating PI3 K/AKT signaling pathway could promote PTEN expression levels, and thereby enhancing paclitaxel sensitivity in NSCLC cells.	[22]
NSCLC	miR-9600 (Down)	BALB/c nude mouse	20 pairs of NSCLC tissues and ANCs	A549, SPC-A-1, H1299, SK-MES-1, NCI-H520, 95D, 16HBE, A549/PR, SPC-A-1/PR	STAT3, Rb, CDK2, cyclin-D1, cyclin-E	STAT3	Overexpression of miR-9600 could decrease paclitaxel and cisplatin sensitivity *via* downregulating STAT3 and enhancing chemotherapy-associated cell death in NSCLC.	[23]
NSCLC	miR-30c (Down)	–	–	A549, H460	MTA1	–	Curcumin *via* overexpression of miR-30c-5p could suppress the expression level of MTA1and thereby could promote the sensitivity of Paclitaxel-resistant NSCLC cells to Paclitaxel.	[21]
NSCLC	miR-107 (Down)	2–4-week-old male BALB/C nude mice	–	A549, HEK293 T, A549/Taxol	Bcl-w	PI3 K/AKT	Upregulation of miR-107 could inhibit paclitaxel resistance NSCLC cells *via* directly suppressing Bcl-w and modulating PI3 K/AKT signaling pathway, and thereby promoting chemosensitivity to paclitaxel and apoptosis, and reducing cell proliferation.	[24]
NSCLC	miR-216b (Down)	–	–	A549, Calu-3	Beclin-1	–	Overexpression of miR-216b levels could downregulate Beclin-1 protein translation and inhibit cell autophagy, and thereby promoting the effect of paclitaxel treatment in NSCLC therapy.	[25]
NSCLC	miR-137 (Down)	6-week-old male BALB/ C nude mice	50 pairs of NSCLC tissues and ANCs	A549, A549/PTX, A549/CDDP, HEK293 T	NUCKS1, HIF-1α, p-Akt	–	Overexpression of miR-137 *via* targeting NUCKS1 could suppress cell proliferation, migration, induced cell apoptosis in NSCLC cells, and thereby promoting the chemosensitivity of paclitaxel and cisplatin in tumor cells.	[26]
NSCLC	miR-203, miR-542-3p (Down)	Athymic nu/ nu mice	20 pairs of NSCLC tissues and ANCs	A549, H460, HEK293 T	DNMT1, Survivin	–	Entinostat could promote the expression levels of miR-203 and miR-542-3p through suppression of HDAC and decreasing DNMT1, thus improving paclitaxel induced growth inhibition and apoptosis in NSCLC cells.	[27]
NSCLC	miR-195 (Down)	female athymic nude Foxn1nu (nu/nu) mice	57 pairs of LUAD tissues and ANCs 51 pairs of LUSC tissues and ANCs	H1993, H358, H1155, H1299, H2073	CHEK1	–	miR-195 synergizes with paclitaxel and eribulin could suppress the expression level of CHEK1, and thereby inhibiting the growth of cancer cells in NSCLC and contributing to sensitize to MTAs.	[28]
NSCLC	miR-186 (Down)	female nude mice	266 pairs of NSCLC tissues and ANCs	293FT, A549, H1299, H1975, H4006, Calu-3, HCC95	MAPT, p53, p21, BCL2	P53	Overexpression of miR-186 *via* directly targeting the expression of MAPT could promote the sensitivity of NSCLC cells to paclitaxel both in vitro and in vivo.	[29]
NSCLC	miR-30a-5p (Down)	BALB/c nu/ nu male mice	94 pairs of NSCLC tissues and ANCs	A549, H460, A549/PR, H460/ PR	BCL-2	–	Upregulation of miR-30a-5p *via* suppressing the expression level of BCL-2 could promote paclitaxel	[30]

(*continued on next page*)

Table 1 (*continued*)

Cancer type	microRNA& Expression Pattern	Animal	Human	Assessed cell line	Targets/ Regulators	Signaling Pathway	Function	Ref
							sensitivity in NSCLC, and thus increasing apoptosis.	
Lung Cancer (LC)	miR-200c (Down)	–	–	A549, A549/TAX	CTSL, Snail, E-cadherin, N-cadherin, Vimentin, cytokeratin-18	–	Upregulation of miRNA-200c in lung cancer cells could suppress the expression of CTSL, and thereby promoting their sensitivity to paclitaxel and significantly inhibiting EMT.	[31]
Lung Cancer Stem Cells (LCSCs)	miR-128 (Down)	female athymic BALB/c nude mice	–	A549, A549-PTX	MUC1-C, MUC1, BMI-1, β-catenin	β-catenin, PI3 K/AKT	Overexpression of miR-128 *via* suppressing the expression levels of MUC1-C and BMI-1 and effectively reducing the levels of β-catenin could promote paclitaxel sensitivity in CSCs, and thereby inhibiting tumorigenicity.	[32]

subunits which is required for polymerization into microtubules and enhances the proportion of tubulin subunits that amass. Besides, microtubules polymerized following treatment with paclitaxel are sheltered from the dissociation typically prompted by exposure to cold or calcium ions [3]. Paclitaxel induces mitotic arrest *via* induction of the mitotic checkpoint, the chief cell cycle regulatory system functioning in the course of mitosis to avoid chromosome mis-segregation [2]. In fact, this chemotherapeutic agent arrests cells in the mitosis as a result of existence of small quantities of unattached kinetochores [4]. The human albumin-stabilized paclitaxel units have a typical size of 130 nm (https://pubchem.ncbi.nlm.nih.gov/compound/Paclitaxel#section=Therapeutic-Uses). In spite of its potent effects against tumoral cells, primary or secondary resistance to paclitaxel occurs in a number of patients precluding its long-term application in these patients. Notably, attainment of resistance to this drug results in the remarkable aggressiveness of cancer cells and poor clinical outcome [5]. Several mechanisms contribute in this phenomenon among them are up-regulation of multidrug resistance proteins, molecular alterations in its cellular targets and alterations in the apoptotic pathways and mitosis checkpoint apparatus [6]. Up-regulation of the multidrug transporter proteins which construct the efflux pumps increases effluxion of paclitaxel outside the cells, thus obstructing drug retaining. Among these proteins are ABCB1 (MDR1) and ABCC1 (MRP1) [7–9]. Moreover, point mutation in the β-tubulin coding gene at the site of paclitaxel attachment is another proposed mechanism for resistance to paclitaxel [10]. Besides, changes in the expression quantities of tubulin isotypes might affect response to this drug [11]. More recently, non-coding RNAs (ncRNAs) have been shown to influence response of cancer cells to paclitaxel [12]. Differential expression of these transcripts between paclitaxel-resistant and –sensitive cancer cells has potentiated ncRNAs as possible culprits in the induction of resistance phenotype [12]. In the present review, we provide a review of studies which assessed the role of two classes of ncRNAs *i.e.* microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) in conferring resistance to paclitaxel.

2. miRNAs and response to paclitaxel

These endogenously produced small RNAs have sizes about 22 nucleotides. They can regulate expression of genes at post-transcriptional level through either cleaving target transcripts or suppressing translation of mRNA to proteins [13]. The interactions between miRNAs and mRNAs are complex processes since a certain miRNA can alter expression of numerous target transcripts and expression of each mRNA might be controlled by several miRNAs [14]. These small-sized molecules regulate cell differentiation, proliferation and apoptotic processes, thus partake in the evolution of human cancers [14]. In addition, they can modulate response of cancer cells to the therapeutic options [15]. In the following sections, the role of miRNAs in the modulation of response of different cancer types will be discussed. Previous researches have detected that ectopic expression of microRNAs could have an important role in causing paclitaxel sensitivity in various human cancer cells *via* modulating some targets. Ma et al. have demonstrated that miR-107 could significantly promote paclitaxel sensitivity in breast cancer cells *via* Wnt/β-catenin cascade by directly targeting the expression levels of TPD52 and cyclin D1 in both mRNA and protein levels. Therefore, this could provide an evidence of modulating paclitaxel effect on breast cancer cells through the role of miR-107 [16]. In addition, Liu et al. also in another study have indicated that upregulation of miR-422a could play a remarkable role in reducing the expression level of TGFβ2 *via* modulating its downstream effectors namely phosphorylated smad 2 and smad3, and thereby could suppress osteosarcoma cell growth and apoptosis as well as paclitaxel and cisplatin resistance in target cells [17]. Another research have illustrated that downregulation of miR-140-3p or miR-155-5p *via* antagomir could suppress the PI3 K-AKT-mTOR signaling pathway activation, thus reducing phosphorylation of Bad, mTOR and Gsk-3β. This could have an effective role in reducing paclitaxel, doxorubicin, and cisplatin resistance in chordoma by directly targeting the expression level of PTEN which could lead to restraining tumor cell survival, invasiveness, EMT and resistance to chemotherapy drug [18]. Fig. 1 illustrates the role of miRNAs in modulation of paclitaxel resistance *via* regulating TGF-β, Smad and Wnt/β-catenin routes.

2.1. Lung cancer

Dysregulation of a number of miRNAs have been noted in cell lines or clinical samples of patients with lung cancer. Moreover, functional studies have shown the effects of miRNAs up- or down-regulation in changing the responsiveness of these cells to paclitaxel. For instance, miR-935 silencing has been shown to enhance expression of SOX7 and increase the anticancer impacts of paclitaxel in lung cancer cells. In addition to its direct effects on expression of SOX7, miR-935 increases levels of Bcl-2 and phosphorylated AKT and reduces expression of the apoptotic protein BAX. Thus, miR-935 has been suggested as a predictor of response of lung cancer cells to paclitaxel [19]. miR-421 as another up-regulated miRNA in lung cancer cells has been shown to inhibit expression of KEAP1 through direct interaction with its 3′-untranslated region (3′UTR). Oligonucleotide-mediated miR-421 silencing has enhanced ROS levels and response of cancer cells to paclitaxel both in cancer cell lines and in xenograft models. Further investigations revealed β-catenin as the main regulator of miR-421 expression in lung cancer [20]. Notably, miRNAs also mediates the drug-sensitizing effects of a number of agents used as herbal medicine. For instance, Curcumin has been shown to enhance the sensitivity of lung cancer cells to

Table 2
Role of miRNAs in the modulation of response of cancers of female reproductive system to paclitaxel (ANCs: adjacent normal controls).

Cancer type	microRNA & Expression Pattern	Animal	Human	Assessed cell line	Targets/ Regulators	Signaling Pathway	Function	Ref
Ovarian Cancer (OC)	miR-23a (Up)	BALB/c nude mice	36 pairs of OC tissues and ANCs	SKOV3, MeyA-8, SKOV3/PTX, MeyA-8/PTX	SNHG5	–	SNHG5 *via* sponging miR-23a could promote the sensitivity of ovarian cancer cells to paclitaxel, and thereby resulting in suppressing cell proliferation and inducing cell apoptosis.	[35]
OC	miR-181a (Up)	–	20 OC tissues and 15 normal ovarian specimens	SKOV3, SKOV3/PTX	E-cadherin, N-cadherin	–	Overexpression of miR-181a resulting in increasing the level of EMT and thereby inhibiting cell apoptosis induced by paclitaxel remedy in ovarian cancer cells.	[33]
OC	miR-17-92 gene cluster (miR-17, miR-92-1, miR-19b, miR-20a) (Up)	–	–	SKOV3, SKOV3-TR30	PTEN, ABCA1, BIM	–	Expression level of the miR-17-92 gene cluster was found to be remarkably upregulated in the paclitaxel-resistant cells in comparison with in the paclitaxel-sensitive cell line.	[27]
OC	miR-27a (Up)	Mouse	–	SKOV3, A2780, HO8910, OVCAR3, PEO-1	HIF-1α, APAF1	HIF-1α	miR-27a *via* downregulating the expression level of APAF1 could contribute to paclitaxel resistance in OC cells induced by hypoxia through HIF-1α.	[36]
OC	miR-1307 (Up)	–	–	SKOV3, SKOV3-TR30	CIC, ETV4, ETV5	RTK	Overexpression of miR-1307 could upregulate the expression levels of ETV4 and ETV5 genes *via* modulating CIC transcription repressor, and thereby promoting the resistance of ovarian cancer cells to paclitaxel.	[37]
OC	miR-1252 (Down)	6-week-old female BALB/c athymic nude mice	36 pairs of OC tissues and ANCs	SKOV3, HeyA-8, IOSE-80, SKOV3/PTX, HeyA-8/PTX	FOXR2, circCELSR1	–	circCELSR1 acts as a molecular sponge to downregulate miR-1252, and thus leading to partial suppression of the expression level of its target gene FOXR2, and is associated with promoting the paclitaxel chemosensitivity and aggressive ovarian cancer phenotypes.	[38]
OC	miR-383-5p (Down)	4-week-old BALB/C athymic nude mice	30 pairs of OC tissues and ANCs	HOSEpiC, SKOV3, A2780, OVCAR-3, Caov-3	TRIM27, Ki67, PCNA	PI3 K/AKT	Overexpression of miR-383-5p could promote paclitaxel based chemosensitivity of ovarian cancer cells and suppress ovarian tumor growth *via* inhibiting the expression level of TRIM27 through PI3 K/AKT pathway.	[39]
OC	miR-1299 (Down)	Nude mice	Mouse/human; 48 pairs of OC tissues and ANCs	SKOV3, HeyA-8, IOSE-80, SKOV3/PTX, MeyA-8/PTX	NEK2, circTNPO3	circTNPO3/ miR-1299/ NEK2	circTNPO3 *via* downregulating miR-1299 and upregulating the expression level of NEK2 could promote paclitaxel resistance in ovarian cancer cells.	[40]
OC	miR-134 cluster (miR-382, miR-409, miR-134, miR-376c, miR-	–	–	SKOV3, SKOV3-TR30	CDC42, MRP1/ ABCC1, c-Myc	–	Expression level of the miR-134 gene cluster was detected to be considerably	[27]

(*continued on next page*)

Table 2 (*continued*)

Cancer type	microRNA & Expression Pattern	Animal	Human	Assessed cell line	Targets/ Regulators	Signaling Pathway	Function	Ref
	379, miR-381, miR-487b, miR-654, miR-409, miR-299, miR-487a, miR-485, miR-154) (Down)						downregulated in the paclitaxel-resistant cell line compared with in the paclitaxel-sensitive cell line.	
OC	miR-7 (Down)	4–6-week-old female BALB/c nude mice	–	HO8910PM	EGFR, ERK1/2	EGFR/ERK	Upregulation of miR-7 could remarkably promote the chemotherapeutic effect of paclitaxel *via* the suppression of PTX-induced EGFR/ERK pathway activation for ovarian cancer remedy.	[41]
OC	miR-136 (Down)	–	44 pairs of OC tissues and ANCs	SKOV3, SKpac-10, SKpac-13, SKpac-16, SKpac-17	Notch3, Bim, Bid, Bax, survivin, DNA-PK, S6, Cyclin D1, NF-kB, BCL2, BCL-XL	NOTCH3	Overexpression of miR-136 *via* downregulating the expression level of Notch3 could promote the sensitivity of ovarian cancer cells to paclitaxel, and thereby restoring chemosensitivity and increasing PTX-induced apoptosis in PTX-resistant OC cells.	[42]
OC	miR-21 (Down)	Female BALB/c athymic nude mice	14 pairs of OC tissues and ANCs	A2780, OVCA432, OVCA433, OVCAR5, HeyA8, HeyA8-MDR, SKOV3ip, SKOV3-TR, SKOV3, PEA1, PEA2	APAF1	TGF-β	Prevention of exosomal transfer of miR21 from stromal cells could inhibit ovarian cancer growth *via* upregulation the expression level of APAF1 in tumor cells, and thereby sensitizing ovarian cancer cells to paclitaxel treatment.	[43]
OC	miR-150 (Down)	–	58 pairs of OC tissues and ANCs	SKOV3, SKpac-10, SKpac-12, SKpac-13, SKpac-16, SKpac-17	Notch3, NICD3, HEY2, cyclinD3, pS6, NF-kB, BCL-2, BCL-W, ALDH1, CD24, CD133, c-Kit, DNA-PK, pS6, S6, cyclin D3, p21, p27, NF-κB, Bad, Bak, Bim, Bid, Bax	NICD3	Overexpression of miR-150 could reduce the expression level of Notch3, and thereby promoting paclitaxel sensitivity in PTX-resistant ovarian cancer cells *via* suppressing proliferation and enhancing apoptosis.	[44]
OC	miR-193b-3p (Down)	–	–	A2780, SKOV3, OVCAR3, HeyC2, HOEC	PAK3	–	Overexpression of miR-193b-3p *via* suppression the expression level of PAK3 could inhibit cell proliferation, and promote paclitaxel-mediated caspase-3 in ovarian cancer cells.	[45]
OC	miR-194-5p (Down)	–	–	SKOV3ip1, HeyA8, SKOV3ip1-TR, HeyA8-TR	MDM2, p21	–	Upregulation of miR-194-5p *via* suppressing the expression level of MDM2 could modulate sensitivity to paclitaxel in OC cell, and thereby inducing G0/G1cell cycle arrest.	[46]
Epithelial ovarian cancer (EOC)	miR-146a (Down)	–	–	OVCAR3, CAOV3, HEY, HOSE	SOD2	–	Upregulation of miR-146a *via* promoting ROS generation and reducing the expression level of SOD2 could improve paclitaxel-induced decrease in cell viability, and thereby suppressing Proliferation and Enhancing Apoptosis and Chemosensitivity.	[47]
EOC	miR-134 (Down)	–	30 patients: 5 with normal ovarian tissues, 7 with serous cystadenoma, 5 with borderline	SKOV3, A2780, COC1, SKOV3-TR30, SKOV3-	ABCC1, LINC01118	–	LINC01118 could promote paclitaxel resistance of EOC cells *via* regulating miR-134/ABCC1, and	[48]

(*continued on next page*)

Table 2 (*continued*)

Cancer type	microRNA & Expression Pattern	Animal	Human	Assessed cell line	Targets/ Regulators	Signaling Pathway	Function	Ref
			cystadenoma, and 13 with serous cystadenocarcinoma	DDP, COC1/ DDP, 293 T			thereby enhancing apoptosis, migration, and invasion in tumor cells.	
EOC	miR-134 (Down)	–	48 pairs of EOC tissues and ANCs	SKOV3, SKOV3-TR30	NF-κB1, c-Rel, ELK1, TAB1	–	Upregulation of NF-κB1, c-Rel and ELK1 could negatively modulates miR-134 expression in serous EOC specimens. Thus, overexpression of miR-134 *via* targeting TAB1 could improve paclitaxel-sensitivity and promote apoptosis in tumor cells.	[49]
EOC	miR-874-3p, miR-874-5p (Down)	–	20 EOC cancerous tissue specimens and 10 normal tissue samples	Caov3, SKOV3	SIK2, XIAP	–	Overexpression of miR-874-3p and miR-874-5p *via* blocking the expression level of SIK2 could promote paclitaxel sensitivity and apoptosis in EOC cells and inhibit proliferation, metastasis, and chemoresistance in cancer cells.	[50]
Cervical Cancer (CC)	miR-21 (Up)	–	–	C-33A, CaSki, SiHa, HeLa, ME-180, TCHu176, TCHu137, TCHu113, TCHu187, TCHu180, H8	Bcl-2, Bax, PDCD4, survivin, c-myc, PTEN, p-AKT	PTEN/AKT	Downregulation of miR-21 could inhibit cell proliferation and colony formation of cervical cancer cells *via* modulating the PTEN/AKT signaling pathway, and thereby improving paclitaxel sensitivity in tumor cells.	[34]
CC	miR-34a (Down)	Female BALB/c nude mice	–	U14	Bcl-2, CDK6	–	The ultrasound-mediated PTX-miR-34a-MBs synergistically could suppress the cervical cancer cell proliferation through overexpression of miR-34a and inhibition of Bcl-2 and CDK6 expression levels.	[51]
CC	miR-125a (Down)	6-week-old female BALB/c nu/nu mice	43 pairs of CC tissues and ANCs	HeLa, CaSki, HeLa/PR, CaSki/PR	STAT3	–	Upregulation of miR-125a could promote paclitaxel and cisplatin sensitivity in CC cells *via* downregulating the expression level of STAT3, and thereby increases apoptosis and microtubule stabilization.	[52]
Endometrial carcinoma (EC)	miR-205-5p (Up)	–	25 pairs of EC tissues and ANCs	NEC, KLE, HEC-1-A, HEC-1-B, RL95-2	FOXO1	–	Downregulation of miR-205-5p *via* negatively targeting FOXO1 could promote paclitaxel sensitivity in EC cells, and thereby repressing cell proliferation and elevating cell apoptosis.	[53]
EC	miR-24 (Down)	–	46 pairs of EC tissues and ANCs	HEC-1A, HEK293 T	S100A8	–	Overexpression of miR-24 *via* inhibiting the expression level of S100A8 could promote chemotherapy sensitivity of EC cells to paclitaxel, and thereby suppressing malignant proliferation.	[54]

paclitaxel *via* up-regulation of miR-30c and subsequent down-regulation of MTA1 [21]. Table 1 summarizes the results of studies which appraised the role of miRNAs in the modulation of response of lung cancer to paclitaxel.

2.2. Female reproductive system

Expression of miR-181a has been shown to be higher in chemo-resistant ovarian cancer tissues compared with chemosensitive samples and normal tissue. Forced over-expression of this miRNA in SKOV3 cells has reduced E-cadherin expression and augmented N-cadherin

Table 3
Role of miRNAs in the modulation of response of breast cancer to paclitaxel (ANCs: adjacent normal controls).

Cancer type	microRNA	Animal	Human	Assessed cell line	Targets/ Regulators	Signaling Pathway	Function	Ref
Breast Cancer (BCa)	miR-520 h (Up)	–	156 pairs of BCa and ANCs	MCF-7, MCF-7/Taxol	OTUD3, PTEN	AKT	Downregulating miR-520 h could result in the upregulation of OTUD3 which considerably could inhibit the proliferation of breast cancer cells and promote paclitaxel-induced cell apoptosis.	[55]
BCa	miR-155-5p (Up)	–	–	MCF-7, MCF-7/PR	TP53INP1	CXCR4	NT21MP, combined with the down expression of miR-155-5p, could promote the expression level of its target gene TP53INP1 and thereby enhancing the sensitivity of the breast cancer cells to paclitaxel.	[56]
BCa	miR-21-5p (Up)	Male BALB/c nude mice	20 pairs of BCa tissues and ANCs	MCF-10A, MCF-7, MDA-MB-231, MCF-7/PTX, MDA-MB-231/PTX	PDCD4	–	Overexpression of PDCD4 and downregulation of miR-21-5p could enhance paclitaxel sensitivity in BCa cells and suppress the progression in PTX-resistant BC cell lines.	[57]
BCa	miR-520 h (Up)	–	146 pairs of BCa tissues and ANCs	MDA-MB-231, MDA-MB-468, Hs578 T, BT483, T47D, MCF-7, MDA-MB-361, MDA-MB-453, HBL-100	DAPK2	–	Downregulation of miR-520 h *via* enhancing the expression level of DAPK2 could promote the sensitivity of paclitaxel in BCa cells, and thereby reducing cancer cell metastasis.	[26]
BCa	miR-107 (Down)	–	35 pairs of BCa and ANCs	MCF-7, MCF-10A	TPD52, Wnt1, β-catenin, cyclin D1	Wnt/ β-catenin	miR-107 by targeting the expression level of TPD52 *via* Wnt/β-catenin signaling pathway could promote paclitaxel sensitivity in breast cancer cells.	[58]
BCa	miR-542-3p (Down)	Athymic nu/nu mice	–	SKBR3, BT474, MDA-MB-453, HCC1954, BT474-HR20	HER2, HER3, Survivin	PI3 K/ AKT, HER3	Upregulation of miR-542-3p could suppress the expression level of Survivin, and thereby blocking HER3/PI-3 K/AKT signaling pathway and remarkably promote the antitumor activity of paclitaxel against HER2-overexpressing breast cancer.	[59]
BCa	let-7a, miR-205 (Down)	–	–	MCF-7, MDA-MB-231, SKBR-3, BT-474	K-RAS, HER3	–	HER2-negative breast cancer cell lines indicates a remarkably downregulated the expression levels of both miR-205 and let-7a after treatment with paclitaxel.	[60]
BCa	miR-140-5p (Down)	BALB/c nude mouse	30 PTX-resistant BC patients and 30 PTX sensitive BC patients	MCF-10A, MCF-7, MDA-MB-231, MCF-7/PTX, MDA-MB-231/PTX	Circ-RNF111, E2F3	–	The suppression effects of circ-RNF111 could result in upregulation of miR-140-5p which thereby could suppress paclitaxel resistance, cell viability, colony formation, cell invasion and glycolysis in PTX resistant BC cells *via* targeting E2F3.	[61]
BCa	miR-4282 (Down)	–	100 pairs of BCa and ANCs	MCF-7, 293 T	Myc, CDK4, PGR	–	Overexpression of miR-4282 *via* targeting Myc could weaken the tumorigenesis, enhancing apoptosis, suppressing the migration and invasion ability of breast cancer cells and also remarkably could promote the sensitivity of breast cancer cells to paclitaxel.	[62]
BCa	miR-22 (Down)	–	40 pairs of BCa and adjacent normal tissues	MCF7, MDM231, HEK293 T	NRAS	–	miR-22 functions as a tumor suppressor *via* downregulating the expression level of NRAS can play an effective role in sensitize breast cancer cells to paclitaxel.	[63]
BCa	miR-193a-5p (Down)	–	–	MDA-MB-231	P53	P53	miR-193a-5p could promote the sensitivity of BC cells to paclitaxel *via* targeting P53 pathway.	[64]
BCa	miR-34a (Down)	–	–	MCF-7, MDA-MB-231, 293 T, MCF-7/	CCND1, β2 M, SNORD-47	–	miR34a, alone or in combination with paclitaxel, has an effective role in suppressing the cancer cell	[65]

(*continued on next page*)

Table 3 (*continued*)

Cancer type	microRNA	Animal	Human	Assessed cell line	Targets/ Regulators	Signaling Pathway	Function	Ref
				PTX, MDA-MB-231/ PTX			viability and proliferation *via* inhibiting the expression level of CCND1 that could improve the sensitivity of cancer cells to chemotherapy.	
BCa	miR-451 (Down)	Female BALB/c nude mice	TCGA dataset	MCF-7, SKBR3, MCF-7/PR, SKBR3/PR	YWHAZ, β-catenin, cyclin D1, c-Myc	β-catenin	miR-451 *via* directly targeting the YWHAZ/β-catenin signaling pathway could promote the sensitivity of breast cancer cells to paclitaxel, and thereby inducing apoptosis and cell-cycle arrest of tumor cells and inhibiting migration and invasion in BC in vitro and in vivo.	[66]
BCa	miR-149-5p (Down)	Female athymic nude mice	–	MDA-MB-231, MDA-MB-231 PTX-resistant	MyD88, BAX, BCL-2	PI3 K/AKT	Overexpression of miR-149-5p could reduce the expression level of MyD88 and thereby promoting the sensitivity of 231/PTX cells to paclitaxel treatment and suppressing the activation of the AKT signaling pathway in 231/ PTX cells.	[67]
BCa	miR-335 (Down)	–	–	MCF-7, SKBR-3, MCF-7/PR, SKBR-3/ PR	SETD8, cyclin D1, c-Myc	Wnt/ β-catenin	NT21MP and miR-335 could mediate paclitaxel-resistant of breast cancer cells partly *via* remarkably downregulation of SETD8 through regulation of Wnt/β-catenin signaling pathway and thereby promoting the sensitivity of PR cells to paclitaxel.	[68]
BCa	miR-155-3p (Down)	–	–	MCF-7, MCF-7/PR	MYD88	CXCR4	NT21MP, combined with the upregulation of miR-155-3p, could suppress the expression level of its target gene MYD88 and thereby improving the sensitivity of the breast cancer cells to paclitaxel.	[56]
BCa	miR-24 (Down)	Female nude BALB/c mice	20 pairs of BCa and ANCs	MCF-7, SKBR3, MCF-7/PR, SKBR3/PR	ABCB9	–	Overexpression of miR-24 could promote the effect of paclitaxel on drug-resistant breast carcinoma cells through targeting ABCB9.	[69]
BCa	miR-16 (Down)	–	Taxol-sensitive (n = 27) and Taxol-resistant (n = 15) breast cancer tissue specimens	MDA-MB-231, MCF-7	IKBKB, c-PARP	–	Overexpression of miR-16 could sensitize breast cancer cells to paclitaxel *via* inhibiting the expression level of IKBKB.	[70]
BCa	miR-17-5p (Down)	–	3 pairs of BCa and ANCs	MCF-7, MDA-MB-231	STAT3, P53, Bax, PARP, Caspase- 3, p21Cip1/ Waf1, p27Kip1,	STAT3/ P53	Overexpression of miR-17-5p could directly inhibit the expression level of STAT3 and upregulate p53 expression, and thereby inducing apoptosis in breast cancer cells by suppressing the STAT3/p53 pathway.	[71]
BCa	miR-155-3p (Down)	Female BALB/c nude mice	10 pairs of BCa tissues and ANCs	MCF-10A, MCF-7, SKBR-3, MDA-MB-231, MCF-7/PR	MYD88, Bcl-2, Bak-1, Bax, Caspase-3	–	Upregulation of miR-155-3p could inhibit the expression level of MYD88, and thereby promote sensitivity of breast cancer cells to paclitaxel which could suppress cell proliferation, invasion, and metastasis of tumor cells.	[72]
BCa	miR-145-5p (Down)	BALB/c nude mice	32 pairs of BCa tissues and ANCs	MCF-10A, MCF-7, MDA-MB-231, MCF-7/PTX, MDA-MB-231/PTX	SOX-2	–	Upregulation of miR-145-5p could suppress the expression level of SOX2, and thereby promoting paclitaxel sensitivity in PTX-resistant BCa cells and reducing proliferation, migration, invasion of tumor cells.	[73]
BCa	miR-485-5p (Down)	Female SCID mice	–	MDA-MB-231, MDA-MB-468, MCF7	Survivin, BIRC5, BCL2, BAX	–	Overexpression of miR-485-5p could downregulate the expression of survivin, and thereby promoting the doxorubicin and paclitaxel sensitivity in BCa cells and	[74]

(*continued on next page*)

Table 3 (*continued*)

Cancer type	microRNA	Animal	Human	Assessed cell line	Targets/ Regulators	Signaling Pathway	Function	Ref
							inhibiting cancer progression, cell proliferation and invasion.	
BCa	miR-30e (Down)	Male BALB/c-nude mice	40 pairs of BCa and ANCs	293 T, MCF-7, MDA-MB-231, MCF10A	IRS1, HIF-1α, VEGF, AKT, ERK1/2	PI3 K/ AKT, MAPK/ ERK	Upregulation of miR-30e *via* negatively targeting IRS1 could suppress the expression levels of HIF-1α and VEGF, and following that could impede the AKT and ERK1/2 signaling pathways. Therefore Promotes chemosensitivity of MDA-MB-231 cells to paclitaxel and reduces cell proliferation, migration, and invasion.	[75]
BCa	miR-152 (Down)	–	18 pairs of BCa tissues and ANCs	MCF7, MDA-MB-231, T47D, MDA-MB-453, MCF10A	β-catenin, PKM2	Wnt/ β-catenin	Upregulation of miR-152 *via* targeting and suppressing both β-catenin and PKM2 expression levels could sensitize BCa cells to paclitaxel chemotherapeutic drug, and thereby inhibiting tumor cell growth.	[76]
BCa	miR-200c-3p (Down)	–	–	MCF-7, MCF-7/Tax	SOX2	–	Overexpression of miR-200c-3p *via* downregulating the expression level of SOX2 could elevate paclitaxel sensitivity in BCa cells and trigger tumor cell apoptosis.	[77]
Triple Negative Breast Cancer (TNBC)	miR-221/ 222 (Up)	–	–	MDA-MB-231	p27Kip1, TIMP3	–	The novel CaP-polymer hybrid nanoparticle system was utilized to promote remedial effects of the co-delivery of miRi-221/222 and paclitaxel for TNBC *via* overexpression of p27Kip1 and TIMP3 tumor suppressor genes, and thus enhancing cytotoxic efficacy of chemotherapeutic drug.	[78]
TNBC	miR-18a (Up)	–	20 pairs of TNBC tissues and ANCs	MDAMB-231 and MDA-MB-468, MCF-10A, MDA-MB-231/ PTX	Dicer	–	Upregulation of miR-18a is associated with the suppression of Dicer expression and thereby can promote paclitaxel resistance in TNBC cells.	[79]
TNBC	miR-18a (Up)	–	–	MDA-MB-231/PTX, MDA-MB-231, MCF-10A	mTOR, p70S6, LC3 I, LC3 II	mTOR	Overexpression of miR-18a could promote autophagy through suppressing mTOR signaling pathway in TNBC cells, and thereby resulting in paclitaxel resistance.	[80]
TNBC	miR-335 (Down)	–	42 pairs of TNBC tissues and ANCs	MDA-MB-231	–	–	Upregulation of miR-335 can promote the sensitivity of TNBC cells to paclitaxel, cisplatin and doxorubicin, and enhance the effect of chemotherapy.	[81]
TNBC	miR-5195-3p (Down)	–	36 pairs of TNBC tissues and ANCs	MCF-7, BT549, MDA-MB-468, MDA-MB-231, MCF-10A, BT549/PTX, MDA-MB-231/PTX	EIF4A2	–	Overexpression of miR-5195-3p could promote the chemosensitivity of triple-negative breast cancer to paclitaxel *via* downregulating EIF4A2.	[82]
TNBC	miR-613 (Down)	–	123 samples of breast cancer tissues and 35 ANCs	MDA-MB-231 TNBC, MCF-7 ER+/PR+, HEK-293 T, SUM1315 TNBC	Daam1, RhoA	Daam1/ RhoA	Upregulation of miR-613 could suppress the expression level of Daam1 and reduce RhoA activity, and thereby promoting the sensitivity of TNBC cells against paclitaxel which could inhibit cell migration, cell invasion and colony formation of TNBC cells.	[83]
TNBC	miR-153-5p (Down)	BALB/c nude mice	–	MCF10A, MDA-MB-231, MDAMB-231/ PTX	CDK1, cyclin B1, p-Akt	–	Upregulation of miR-153-5p could remarkably promote paclitaxel sensitivity in BCa cells *via* inducing G2/M phase arrest and downregulating the expression levels of CDK1, cyclin B1 and p-Akt.	[84]
TNBC	miR-1180 (Down)	NOD/SCID mice	normal tissues (n = 113), primary	MDA-MB-231, MDAMB468,	OTUD7B, CASP3	NF-κB	Overexpression of miR-1180 could downregulate the	[85]

(*continued on next page*)

Table 3 (*continued*)

Cancer type	microRNA	Animal	Human	Assessed cell line	Targets/ Regulators	Signaling Pathway	Function	Ref
			tumors (n = 1061) and metastatic tumors (n = 7) from Heatmap data	HCC1806, HCC1937, HCC38, HCC70, BT-20, Hs578t			expression level of OTUD7B, and thereby enhancing paclitaxel sensitivity in TNBC cells *via* suppressing NF-κB activity which in turn triggers Let-7 microRNA-mediated caspase-3 upregulation.	
Minimally Transformed Mammary Epithelial Breast Cancer Cells (MTMECs)	miR-106b-25 (Up)	–	–	MTMEC-ev, MTMEC-miR-106b~25, MTMEC-shEP300, MTMEC-shCDH1	EP300, E-cadherin	–	Upregulation of miR-106b~25 cluster *via* suppressing the expression levels of EP300 and E-cadherin could lead to resistance to etoposide, colchicine and paclitaxel through apoptosis evasion.	[17]
Breast Cancer Stem Cells (BCSC)	miR-200c (Down)	–	–	MCF-7	TUBB3	–	miR-200c delivered *via* solid lipid nanoparticles (SLN) could sensitize the cytotoxicity of NLC/PTX against BCSC through negatively regulating TUBB3 expression.	[86]
Luminal A Breast Cancer	miR-100 (Down)	8-week-old female BALB/c nude mice	36 pairs of BCa tissues and ANCs	T-47D, MCF-7, ZR-75-1, BT-549, MDA-MB-231, Hs578T	mTOR	–	Overexpression of miR-100 *via* targeting mTOR could promote the sensitivity of breast cancer cells to paclitaxel, and thereby suppressing cell proliferation and survival of tumor cells and enhancing the effect of paclitaxel on cell cycle arrest, multinucleation and apoptosis.	[87]

expression. Such effects have been accompanied by induction of chemoresistance in these cells [33]. Another study in ovarian cancer cells revealed down-regulation of the miR-134 gene cluster while up-regulation of the miR-17-92 gene cluster in the paclitaxel-resistant cells compared with sensitive cells. Assessment of the expression of targets of these miRNAs in the mentioned cell lines showed differential expression of these proteins among paclitaxel-resistant and –sensitive cells, further highlighting the role of these miRNA clusters in the modulation of response of ovarian cancer cells to paclitaxel [27]. In cervical cancer cells, miR-21 silencing has enhanced cell apoptosis, inhibited cell proliferation, decreased expression of Bcl-2, survivin, c-myc and p-AKT while increased expression of Bax, PDCD4 and PTEN. Moreover, knock down of this miRNA enhanced anticancer effects of paclitaxel in these cells [34]. Table 2 summarizes the results of studies which assessed the role of miRNAs in the modulation of response of cancers of female reproductive system to paclitaxel.

2.3. Breast cancer

Forced over-expression of miR-520 h in MCF-7 breast cancer cells has enhanced cell proliferation and suppressed paclitaxel-induced cell apoptosis. On the other hand, silencing of miR-520 h promoted the paclitaxel sensitivity in the resistant cells. Mechanistically, this miRNA targets OTUD3 to modulate paclitaxel resistance in these cells. Furthermore, miR-520 h suppresses PTEN expression *via* OTUD3 and consequently influences function of downstream p-AKT pathway [55]. A microarray study has shown down-regulation of miR-155-3p while up-regulation of miR-155-5p in paclitaxel-resistant breast cancer cells compared with parental cells. A 21-residue peptide namely NT21MP has been shown to combat paclitaxel-resistance phenotype of breast cancer cells *via* targeting miR-155-3p and miR-155-5p through the CXCR4 pathway [56]. miR-21-5p is another up-regulated miRNA in paclitaxel resistant breast cancer cell lines. This miRNA has been shown to directly target PDCD4. Knock down of this miRNA reduces paclitaxel resistance and suppresses cancer cell progression *via* up-regulation of PDCD4 [57]. Table 3 shows the role of miRNAs in the modulation of response of breast cancer to paclitaxel.

2.4. Gastrointestinal (GI) cancers

Several studies have been shown a disease-modifying and prognosis determining effect and microRNAs in colorectal cancer [88,89]. miR-29a has been shown to contribute in both evolution of colorectal cancer and resistance of these cells to chemotherapeutic agent, paclitaxel. This miRNA inhibits expression of PTEN. Expression of this miRNA has been up-regulated paclitaxel resistant colorectal cancer cells. Inhibition of expression of this miRNA leads to over-expression of PTEN, suppression of p-AKT, attenuation of cell proliferation, and enhancement of apoptosis paclitaxel resistant cells [90]. Exosomal miR-522 has been shown to inhibit expression of ALOX15, a gene which is implicated in the production of lipid-ROS in gastric cancer. Such exosomes are mainly originated from cancer-associated fibroblasts in tumor microenvironment. Notably, cisplatin and paclitaxel enhance miR-522 secretion from these fibroblasts through stimulating USP7/hnRNPA1 axis, resulting in ALOX15 inhibition, reduction of lipid-ROS buildup and diminished sensitivity to the chemotherapeutic agents [91]. miR-16 is another miRNA whose expression has been down-regulated in the hepatocellular carcinoma samples and cell lines. Down-regulation of miR-16 has been shown to confer chemoresistance through modulation of IKBKB and NF-κB signaling pathway [92]. Table 4 summarizes the results of studies which assessed the role of miRNAs in the modulation of response of GI cancers to paclitaxel.

2.5. Prostate cancer

The anti-cancer flavonoid morin has been shown to suppress the cell viability of paclitaxel-treated prostate cancer cells possibly *via* down-regulation of miR-155. This miRNA has been reported to directly suppress GATA3 expression. Therefore, morin has been suggested as a possible adjuvant of paclitaxel in treatment of prostate cancer which exerts its role *via* modulating miR-155/GATA3 axis [98]. Expression of miR-199a has been decreased in prostate cancer samples, especially recurrent ones. This miRNA has also been suppressed in paclitaxel-resistant cells. Forced up-regulation of this miRNA reverses paclitaxel resistance in these cells *via* modulating expression of YES1. Therefore, this miRNA has the capacity for combating paclitaxel

Table 4
Role of miRNAs in the modulation of response of GI cancers to paclitaxel (ANCs: adjacent normal controls).

Cancer type	microRNA	Animal	Human	Assessed cell line	Targets/ Regulators	Signaling Pathway	Function	Ref
Colorectal Cancer (CRC)	miR-29a (Up)	–	–	CCD841 CoN, SW480, HEK293 T, SW480/ Paclitaxel	PTEN	PI3 K/AKT	Downregulation of miR-29a could promote the expression level of PTEN, and thereby resulting in suppressing CRC cell proliferation, facilitating apoptosis, and diminishing drug resistance.	[90]
CRC	miR-143 (Down)	–	–	SW48, LoVo	KRAS	KRAS	miR-143 can remarkably promote the sensitivity of tumor cells harboring mutant KRAS to treatment with paclitaxel and thereby enhancing the chemosensitivity, which can play an effective role in treating cancers with mutant KRAS.	[93]
CRC	miR-203 (Down)	–	10 pairs of CRC tissues and ANCs	CCD-18Co, CCD-33Co, LoVo, CaCo-2, T-84, SW480, DLD-1, NCIN87, SKBR3, LNCaP, SK-MEL-30, SW-1271, SKOV3, HT-29	SIK2	–	Upregulation of miR-203 could promote the sensitivity of colon cancer cells to paclitaxel and other anti-cancer agents *via* suppressing the expression level of SIK2.	[94]
Gastric cancer (GC)	miR-522 (Up)	6–8-week-old male BALB/c-nu nude mice	45 pairs of GC tissues and ANCs and plasma samples	SGC7901, MGC803, MKN45	ALOX15, hnRNPA1, USP7, lipid-ROS, α-SMA, FAP, FSP1, D63, Alix, Tsg101, PABPC1, ACO1	USP7/ hnRNPA1	Blocking USP7 or hnRNPA1 could remarkably suppress the expression level of miR-522 *via* modulating USP7/hnRNPA1 pathway leading to ALOX15 overexpression and increased lipid-ROS accumulation in tumor cells, and eventually result in promoting sensitivity to paclitaxel in GC cells.	[91]
GC	miR-26b (Down)	–	–	GES-1, BGC823, SGC7901, HEK293 T, SGC7901/PA	CDC6	–	miR-26b could suppress growth and resistance to paclitaxel chemotherapy through repressing the expression level of CDC6 in the gastric cancer cells.	[95]
GC	miR-34a (Down)	–	–	MKN45, BGC823	E2F5	–	Overexpression of miR-34a could promote the chemotherapeutic efficacy of paclitaxel in gastric cancer cells *via* suppressing the expression level of E2F5.	[96]
GC	miR-34c (Down)	–	74 pairs of GC tissues and ANCs	BGC-823, MGC-803, SGC-7901, GES-1	E2F1	–	Downregulation of E2F1 could enhance the expression level of miR-34c, and thereby promote the sensitivity to paclitaxel combined with cisplatin in GC cells which could inhibit the proliferation of GC cells and apoptosis.	[97]
Hepatocellular Carcinoma (HCC)	miR-16 (Down)	4–5-week-old male BALB/c nude mice	–	SMMC-7721, PLC, BEL-7402, BEL-7404, HepG2, HCCLM3, LO2	IKBKB, MDR1, Caspase 3, PARP	NF-kB	miR-16 by targeting IKBKB could improve paclitaxel sensitivity of HCC cells *via* modulating NF-kB signaling pathway.	[92]

resistance in prostate cancer [99]. Table 5 summarizes the role of miRNAs in the modulation of response of prostate cancer to paclitaxel.

2.6. Other cancers

In addition to the mentioned cancer types, miRNAs modulate response of other types of cancers to paclitaxel. For instance, suppression of miR-140-3p or miR-155-5p in chordoma cell has decreased the malignancy of these cells, reduced activity of PI3 K-Akt-mTOR pathway, and enhanced anti-cancer effects of paclitaxel through up-regulation of PTEN protein level [18]. Expression of miR-9-3p (miR-9) has been shown to be decreased in adriamycin (ADR)-resistant K562/ADR cells and chronic myeloid leukemia patients with multidrug resistant phenotype. Forced up-regulation of this miRNA could attenuate cancer cell resistance to several chemotherapeutic agents both in vitro and in animal models. This miRNA has been shown to target ABCB1 [102]. Table 6 summarizes the results of studies which assessed the role of miRNAs in the modulation of response of other cancers to paclitaxel.

2.7. Prognostic value of paclitaxel-associated miRNA in cancers

Consistent with the role of miRNAs in the modulation of response to paclitaxel, these miRNAs can alter patients' outcome. For instance, over-expressions of miR-520 h, miR-522 and miR-421 have been associated with poor outcome of patients with breast cancer, gastric cancer and lung cancer, respectively (Table 7). On the other hand, up-regulations of miR-4282 and miR-137 confer better survival of patients with breast cancer and lung cancer, respectively (Table 7).

3. LnRNAs and response to paclitaxel

LncRNAs can control important cellular functions *via* interplay with several types of biomolecules such as proteins, chromatin and RNA. They can interact with the epigenetic apparatus and recruit a number of associated proteins to specific loci, modulating methylation marks of DNA or epigenetic marks of histones. With diverse regulatory roles on gene expression, they contribute in the pathogenesis of several kinds of cancers [106]. Moreover, they alter response of cancer cells to

Table 5
Role of miRNAs in the modulation of response of prostate cancer to paclitaxel.

Cancer type	microRNA	Animal	Human	Assessed cell line	Targets/ Regulators	Signaling Pathway	Function	Ref
Prostate Cancer (PCa)	miR-155 (Up)	Nude mice	–	DU145, PC-3	GATA3, PAK2, XRN1	–	Morin could remarkably improve chemo-sensitivity of prostate cancer cells to paclitaxel *via* recovering the expression of GATA3 and downregulation of miR-155.	[98]
PCa	miR-34a (Down)	8-week-old male nude mice	–	LNCaP, C4-2, DU145, PC3, RWPE-1, DU145-TXR, PC3-TXR	SIRT1, cyclin D1, E-cadherin, P53, Bax	TAp73, Elk-1, and p53-independent pathway	Rubone can play an effective role as an efficient small-molecule modulator of miR-34a to suppress chemoresistance and thereby promote the therapeutic effect of paclitaxel.	[100]
PCa	miR-34a (Down)	5-week-old female athymic nude mice	TCGA database	PC-3, PC-3PR	JAG1, ADAM17, Notch1, NICD, Bcl2, Cyclin D1, CDK6, c-MYC	Notch1	miR-34a could inhibit paclitaxel resistance in prostate cancer cells *via* downregulating the expression levels of JAG1 and Notch1.	[101]
PCa	miR-199a (Down)	BALB/c nude male mice	28 normal prostate and 74 prostate cancer specimen	PC3, PC3/TXR	YES1	–	Overexpression of miR-199a by downregulation the expression level of YES1 could promote the sensitivity of cancer to PTX treatment in prostate cancer and thereby inducing chemosensitivity to paclitaxel.	[99]

Table 6
Role of miRNAs in the modulation of response of other cancers to paclitaxel.

Cancer type	microRNA	Animal	Human	Assessed cell line	Targets/ Regulators	Signaling Pathway	Function	Ref
Chordoma	miR-140-3p, miR-155-5p (Up)	NU/NU nude mice	Chordoma tissue specimens and nucleus pulposus tissues of 3 patients	–	PTEN, Bad, Gsk-3β	PI3 K-AKT-mTOR	Downregulation of miR-140-3p or miR-155-5p through suppressing PI3 K-AKT-mTOR signaling pathway could sensitize patient-derived chordoma cells to paclitaxel, doxorubicin, and cisplatin *via* PTEN overexpression, and thus inhibiting chordoma cell survival, invasiveness, EMT and resistance to chemotherapy.	[18]
Chronic Myelogenos Leukemia (CML)	miR-9 (Down)	4-week-old male athymic nude mice	blood samples of 61 CML patients	K562, K562/ ADR	ABCB1	–	Upregulation of miR-9 by directly targeting ABCB1 could sensitize CML cells to chemotherapy, and thereby promoting sensitivity in tumor cells to doxorubicin, vincristine, and paclitaxel.	[102]
Osteosarcoma (OS)	miR-422a (Down)	–	20 OS and 14 normal tissues	MG-63, Saos-2, U-2 0S, hFOB	TGFβ2, smad2, smad3	TGFβ2/ smad	Upregulation of miR-422a *via* suppressing the expression level of TGFβ2 could lead to downstream effector regulation containing phosphorylated smad 2 and smad3 to attenuate OS proliferation and invasion, and thereby promoting paclitaxel and cisplatin-mediated apoptosis in OS cells.	[17]
Nasopharyngeal carcinoma (NPC)	miR-29c (Down)	6-week-old male BALB/ c nude mice	–	SUNE-1, C666-1, SUNE-1-Taxol, C666-1-Taxol	ITGB1, MDR1, Caspase-3, Bcl-2, BAX	–	Overexpression of miR-29c could downregulate the expression levels of ITGB1 and MDR1, and thereby improving the sensitivity of NPC cells in response to Taxol treatment and promoting apoptosis in Taxol-resistant NPC cells.	[103]
Glioma	miR-34a (Down)	–	21 pairs of glioma and adjacent normal tissues	U251, U87-MG, U87-P	PD-L1	–	Upregulation of miR-34a *via* suppressing the expression level of PD-L1 could promote paclitaxel sensitivity in glioma cells, and thereby inhibiting tumor cell proliferation and apoptosis.	[104]
Bladder Cancer (BLC)	miR-448 (Up)	–	–	EJ	Bcl-2	–	Paclitaxel combined with miR-448 can promote paclitaxel-induced bladder cancer EJ cell apoptosis and suppress cell proliferation *via* targeting Bcl-2.	[105]

chemotherapeutic agents such as paclitaxel. In the following sections, we describe the role of lncRNAs in the modulation of response of cancer cells to this drug. Previous studies have demonstrated that the remarkable role of dysregulated lncRNAs in causing tumor cell growth, tumor metastasis as well as chemotherapy resistance. Han et al. have indicated that downregulation of lncRNA H19 could play an important role in promoting sensitivity to paclitaxel in TNBC cells by directly modulating AKT signaling pathway and overexpression of apoptotic regulatory

Table 7
Prognostic value of paclitaxel-associated miRNA in cancers (OS: overall survival, DFS: disease-free survival, RFS: relapse-free survival, CC: cervical cancer, OC: ovarian cancer, BCa: breast cancer, TNBC: triple negative breast cancer, NSCLC: Non-small cell lung cancer, GC: gastric cancer, ANCs: adjacent normal controls).

Sample Number	Kaplan-Meier Analysis	Multivariate Cox Regression	Ref
156 pairs of BCa and ANCs	Higher expression of miR-520 h was associated with poorer OS rate.	Higher expression of miR-520 h was associated with tumor size, histological grade, lymph node metastasis.	[55]
100 pairs of BCa tissues and ANCs	Patients with miR-4282 negative expression had lower OS rate.	Lower expression of miR-4282 was associated with tumor stage and tumor metastasis.	[62]
43 pairs of CC tissues and ANCs	Lower expression of miR-125a was associated with poorer OS rate.	Lower expression of miR-125a was associated with poorer FIGO stage and tumor size.	[52]
45 pairs of GC tissues and ANCs and plasma samples	Higher expression of miR-522 was associated with poorer OS rate.	–	[91]
50 pairs of NSCLC tissues and ANCs	Lower expression of miR-137 was associated with poorer OS and DFS rates.	–	[26]
266 pairs of NSCLC tissues and ANCs	Patients with higher expression of miR-186 had better OS rate.	Lower expression of miR-186 was associated with lymph node metastasis and tumor stage.	[29]
94 pairs of NSCLC tissues and ANCs	Lower expression of miR-30a was associated with poorer OS and DFS rates.	–	[30]
10 NSCLC serum samples and 10 non-tumor serum specimens	Higher expression of miR-421 was associated with poorer OS rate.	Higher expression of miR-421 was associated with smoking history, tumor stage, and pathological patterns.	[20]
48 pairs of OC tissues and ANCs	Higher expression of circTNPO3 was associated with poorer OS rate.	Higher expression of circTNPO3 was associated with FIGO stage and histological type.	[40]
44 pairs of OC tissues and ANCs	Lower expression of miR-136 was associated with poorer OS rate.	–	[42]
TCGA database	Lower expression of miR-34a was associated with poorer OS rate.	–	[101]
42 pairs of TNBC tissues and ANCs	Lower expression of miR-335 was associated with poorer OS rate.	–	[81]

proteins like Bax, Bcl-XL, and Bcl-2. As a consequence it can lead to triggering apoptosis in target cells [107]. Another research have illustrated that downregulation of lncRNA SNHG6 could elevate the expression level of miR-186 and thus reducing paclitaxel resistance in prostate cancer cells as well as tumor cell proliferation and invasion. In addition the knockout of SNHG6 could lead to inhibiting the expression levels of Vimentin, CyclinD1, MMP9, Snail, and ZEB1 and promoting the level of E-cadherin in PCa cells chemotherapy resistance [108]. Additionally, Wang et al. have illustrated that suppression of expression Level of lncRNA SNHG12 could upregulate the expression of miR-181a through directly regulating MAPK/Slug signaling cascade as well as modulating MAPK1 and MAP2K1 which can lead to blocking apoptosis in NSCLC tumor cells [109]. Fig. 2 represents the dysregulation of various types of lncRNAs which negatively modulate expression of target genes through the PI3 K/AKT/mTOR and MAPK/ERK signaling pathways leading to decreasing paclitaxel sensitivity in human cancer cells and causing poor response to treatment.

3.1. Lung cancer

KCNQ1OT1 is an up-regulated lncRNA in lung adenocarcinoma tissues and cell line. Notably, over-expression of this lncRNA has been correlated with malignant features of this cancer. Its silencing has suppressed lung cancer cell proliferation and invasion and induced apoptosis in these cells. This lncRNA has higher expression levels paclitaxel resistant patients compared with paclitaxel responsive ones. KCNQ1OT1 silencing also suppressed expression of MDR1 protein in lung cancer cells [110]. NEAT1 is another up-regulated lncRNA in paclitaxel-resistant lung cancer cells line. Knockdown of this lncRNA ameliorated the paclitaxel-resistance phenotype *via* induction of apoptosis through enhancing expression levels of cleaved PARP and cleaved caspase-3. Besides, NEAT1 has a role in activation of the Akt/mTOR pathway through up-regulation of p-Akt, p-mTOR, Bcl-2 and down-regulation of Bax [111]. Table 8 summarizes the results of studies which assessed the role of lncRNAs in the modulation of response of lung cancers to paclitaxel.

3.2. Female reproductive system

In paclitaxel resistant ovarian cancer cells, NEAT1 has been up-regulated. This lncRNA serves as a molecular sponge for miR-194 to decrease its bioavailability. NEAT1 silencing has reversed paclitaxel resistance and enhanced paclitaxel-induced apoptosis in cell lines and animal models. NEAT1 exerts its effects through up-regulation of ZEB1, the molecular target of miR-194 [114]. In cervical cancer samples, over-expression of LINC00511 has been associated with the tumor stage, tumor size and lymph node involvement. Knock down of this lncRNA in cervical cancer cells has led to down-regulation of MRP1, P-GP, Bcl-2, MMP-2 and MMP-9, while up-regulation of Bax and cleaved-caspase-3 levels. Besides, LINC00511 knock down enhanced sensitivity of these cells to paclitaxel and decreased viability, proliferation, migration and invasion of these cells [115]. Table 9 summarizes the role of lncRNAs in the modulation of response of cancers of female reproductive system to paclitaxel.

3.3. Head and neck cancers

In nasopharyngeal cancers, up-regulation of n375709, CCAT1 and H19 has been associated with paclitaxel resistance [126–128]. Mechanistically, CCAT1 serves as a molecular sponge for miR-181a. miR-181a has been identified as a regulator of paclitaxel resistance that modulates apoptosis through targeting CPEB2 [126]. Table 10 summarizes the results of studies which assessed the role of Role of lncRNAs in the modulation of response of head and neck cancers to paclitaxel.

3.4. Breast cancer

The importance of lncRNAs in conferring resistance to paclitaxel has been evaluated in breast cancer cells, principally in triple negative breast cancer (TNBC). For instance, expression of lncRNA H19 has been higher in paclitaxel-resistant compared with paclitaxel-sensitive cell lines. Its silencing has enhanced sensitivity of sensitivity of paclitaxel-resistant TNBC cells to this agent through modulating the AKT signaling pathway [107]. LINC00511 is another up-regulated lncRNA in breast cancer tissues and cell lines. Notably, up-regulation of this lncRNA has been associated with up-regulation of CDK6, while down-regulation of miR-29c. LINC0051 has direct interaction with miR-29c to decrease its expression. LINC00511 silencing improves sensitivity of breast carcinoma cells to paclitaxel through increasing miR-29c levels and subsequently decreasing CDK6 levels [129].

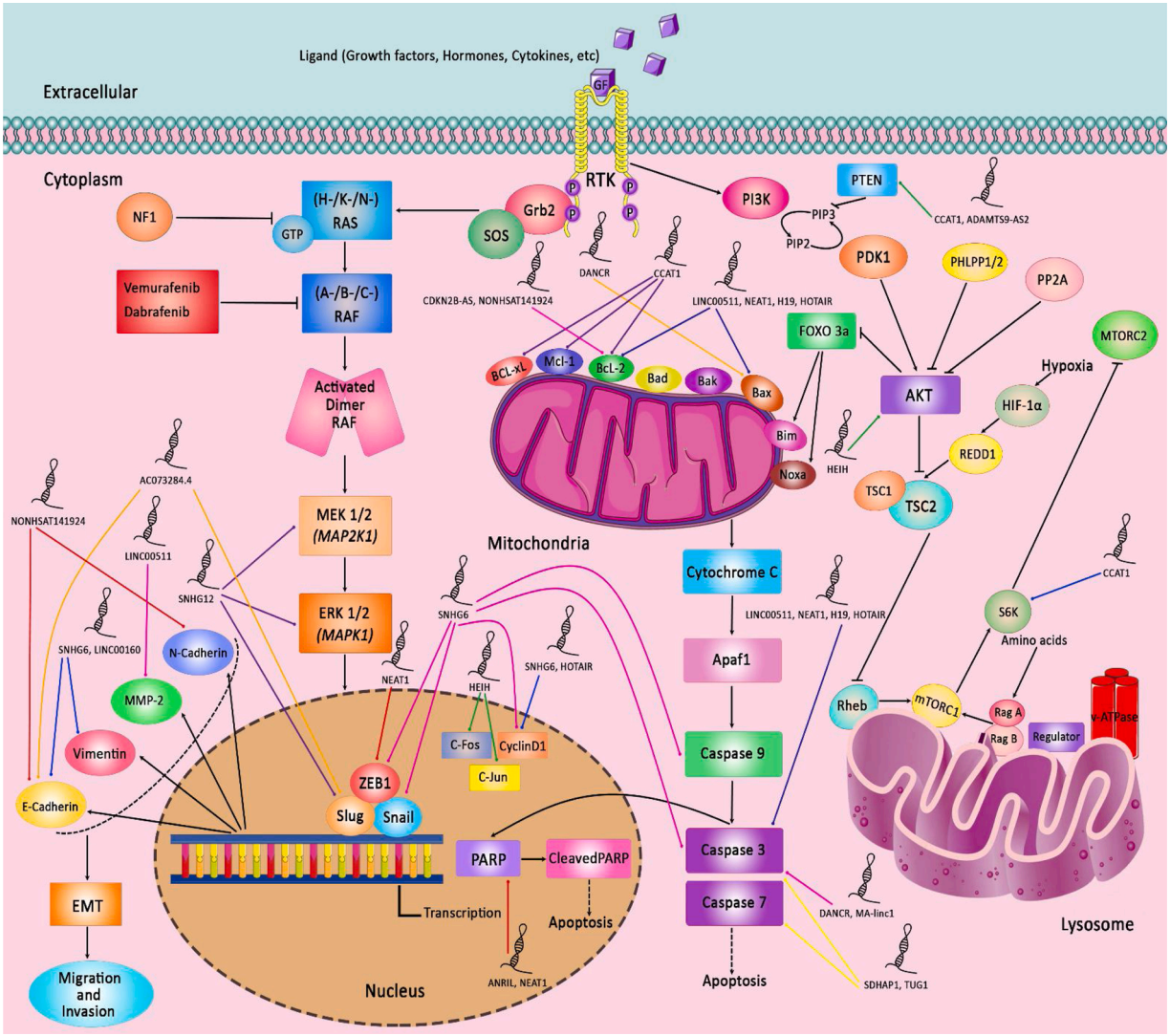

Fig. 2. A schematic illustration of lncRNAs in modulation of ensitivity of human cancer cells to paclitaxel *via* the PI3 K/AKT/mTOR and MAPK/ERK signaling pathways. Ectopic expression of lncRNAs could significantly reduce the phosphorylation of PI3 K, AKT and mTOR, indicating the role of these lncRNAs in the modulation of paclitaxel resistance through suppressing the PI3 K/AKT/mTOR pathway. Alteration of the mitochondrial apoptotic pathway including BCL-2, BCL-xL, Mcl-1, and Bax can also be associated with paclitaxel resistance in various cancer cells *via* aberrant expression of some lncRNAs. Besides, some lncRNAs can affect phosphorylated MEK1/2 and ERK1/2 and induce resistance to paclitaxel through MAPK/ERK pathway. Furthermore, triggering EMT *via* the abnormal expression of lncRNAs could be associated with upregulation of N-cadherin followed by the overexpression of vimentin and downregulation of E-cadherin, and thereby enhancing metastasis, tumorigenesis, and resistance to paclitaxel in target cells.

Table 8
Role of lncRNAs in the modulation of response of lung cancers to paclitaxel (ANCs: adjacent normal controls).

Type of Cancer	lncRNAs & Expression Pattern	P Value	Animal	Clinical Samples (Human)	Cell Lines	Target	Pathway	Observation	Ref
Lung Adeno carcinoma (LAD)	KCNQ1OT1 (Up)	P<0.05	–	76 pairs of LAD and ANCs	16HBE, A549, A549/PA	MDR1	–	Knockdown of KCNQ1OT1 could depress chemoresistance to paclitaxel in LAD.	[110]
LAD	ANRIL (Up)	P<0.05	–	50 pairs of LAD and ANCs	A549/Taxol, A549	Bcl-2, PARP	–	ANRIL *via* the mitochondrial pathway by modulating the cleaved-PARP and Bcl-2 proteins could promote the acquisition of chemoresistance in paclitaxel.	[112]
LAD	ENST00000500843 (Down)	P<0.05	–	56 pairs of LAD and ANCs	A549, A549/PTX	–	–	ENST00000500843 could promotes chemoresistance to paclitaxel in LAD.	[113]
Non-Small Cell Lung Carcinoma (NSCLC)	NEAT1 (Up)	P<0.05	Male BALB/c nude mouse	–	PC-9, H1573, H1299, A549, BE, A549/PTX, A549/PTX	PARP, Caspase-3, Bax, Bcl-2	AKT/mTOR	NEAT1 *via* activating the Akt/mTOR signaling pathway could mediate the paclitaxel-resistance of NSCLC.	[111]
NSCLC	SNHG12 (Up)	P<0.05	Male athymic nude mouse	22 pairs of NSCLC and ANCs	HBE, PC-9, A549, H1299, H358, A549/PTX, A549/DDP, PC9/AB2	miR-181a, MAPK1, MAP2K1, Slug	–	SNHG12 by inducing apoptosis *via* modulating MAPK/Slug pathway through sponging miR-181a and releasing MAPK1 and MAP2K1 could act as an oncogene in NSCLC multidrug resistance.	[109]

Table 11 summarizes the results of studies that assessed the role of lncRNAs in the modulation of response of breast cancer to paclitaxel.

3.5. GI cancers

Expression levels of lncRNAs can also modulate response of colorectal cancer, gastric cancer and liver cancer cells to paclitaxel. In gastric cancer, HOTAIR up-regulation has been associated with paclitaxel and doxorubicin resistance. This lncRNA has been up-regulated in gastric cancer tissues particularly those obtained from advanced stages. Forced over-expression of HOTAIR has augmented cell proliferation, promoted cell cycle progression, enhanced migration and confers resistance to paclitaxel *via* suppressing miR-217 expression and increasing expression levels of GPC5 and PTPN14 [137]. The role of this lncRNA in enhancing chemoresistance in hepatocellular carcinoma is exerted through interaction with miR-34a [138]. Table 12 summarizes the role of lncRNAs in the modulation of response of GI cancers to paclitaxel.

3.6. Prostate cancers

DANCR has been shown to target and miR-135a and suppress its expression in prostate cancer cells. miR-135a is a tumor suppressor miRNA that inhibits cell proliferation, enhances cell apoptosis and promotes paclitaxel sensitivity in these cells. Therefore, DANCR silencing represents a novel strategy for increasing paclitaxel sensitivity in prostate cancer cells [140]. Linc00518 is another up-regulated lncRNA in prostate cancer. Over-expression of this lncRNA has been linked with paclitaxel resistance. Linc00518 acts as a molecular sponge for miR-216b-5p to inhibit its expression [141]. Table 13 summarizes the role of lncRNAs in the modulation of response of prostate cancer to paclitaxel.

3.7. Other cancers

MA-linc1 is an lncRNA whose suppression affects cell cycle distribution, resulting in a reduction in the quantities of G1 cells and a simultaneous upsurge in all other stages of the cell cycle, particularly G2/M. Therefore, this lncRNA is involved in the regulation of M phase. MA-linc1 silencing suppresses M phase exit due to the induction of freedom from a mitotic block. MA-linc1 mainly acts in cis to suppress transcription of its adjacent gene, Purα. Suppression of MA-linc1 increases paclitaxel-associated cell apoptosis through modulation of Purα. Over-expression of MA-linc1 has eben associated with poor clinical outcome in breast and lung cancer patients [142]. Table 14 summarizes the results of studies which assessed the role of lncRNAs in the modulation of response of other cancers to paclitaxel.

3.8. Prognostic value of paclitaxel-associated miRNA in cancers

Expression levels of several lncRNAs that modulate response of cancer cells to paclitaxel have been associated with clinical outcome of cancer patients. For instance, over-expressions of ANRIL, HOTAIR, TUG1, LINC00511 and LINC00160 confer poor overall survival in different cancer types. On the other hand, down-regulations of ENST00000500843, ADAMTS9-AS2 and TCL6 were associated with poor clinical outcome of patients (Table 15).

4. Designing CRISPR/Cas9 System to overcome resistance to paclitaxel

Clinical evidence demonstrated that paclitaxel resistance is a main hurdle in the treatment of different types of human cancers which causes the disease out of control and leads to high mortality [145–147]. Tumor cells attain resistance to multiple chemotherapeutic agents after repeated remedies, which is a serious obstacle to attain efficient cancer therapy. Multiple mechanisms are involved in the development of paclitaxel resistance. These mechanisms include DNA repair cascades mutation, ectopic expression of miRNAs, aberrant expression of long non-coding RNAs, resistance to the starting of the apoptotic cascade, and the promotion of ceaselessly activated signaling pathways, and transforming drug metabolism [148–152]. For instance, ectopic expression of NF-κB1, c-Rel, and ELK1 could lead to TAB1 upregulation that in turn play an important role in downregulating and/or inhibiting the expression level of miR-134 and confer resistance of serous epithelial ovarian cancer cells to paclitaxel [153]. It is remarkably practical to modulate the genome with the clustered regularly interspaced short palindromic repeats (CRISPR)/associated (Cas) 9 technology. Being currently developed, it might play an important role in enhancing paclitaxel sensitivity in cancer cells [154–156]. The conventional mechanism to reduce attained drug resistance is to synthesize agents by adding to different targets. These approaches of sensitizing tumor cells interact with each other, and the efficacy can be difficult to predict.

Table 9
Role of lncRNAs in the modulation of response of cancers of female reproductive system to paclitaxel (ANCs: adjacent normal controls).

Type of Cancer	lncRNAs & Expression Pattern	P Value	Animal	Clinical Samples (Human)	Cell Lines	Target	Pathway	Observation	Ref
Ovarian Cancer (OC)	NEAT1 (Up)	P<0.05	Male BALB/c athymic nude mouse	Treatment-resistant (n = 14) and treatment-responsive (n = 18) patients	SKOV3, HeyA-8, SKOV3/PTX, HeyA-8/PTX	miR-194, ZEB1, GST-π, P-gp	–	Knockdown of NEAT1 *via* targeting the ZEB1/miR-194 axis could enhance PTX sensitivity in PTX-resistant OC cells.	[114]
OC	LINC01118 (Up)	P<0.01	–	30 pairs of OC and ANCs	SKOV3-TR30, A2780, 293 T, COC1, SKOV3-DDP, COC1/DDP	miR-134, ABCC1	–	LINC01118 by regulating miR-134/ABCC1 could modulate paclitaxel resistance of epithelial OC.	[116]
OC	UCA1 (Up)	P<0.05	–	–	SKOV3, HeyA-8, 293 T, SKOV3/PTX, HeyA-8/PTX	ABCB1, miR-129	–	Knockdown of UCA1 by inhibiting miR-129 and targeting ABCB1 could sensitize PTX-resistant OC cells to PTX.	[117]
OC	UCA1 (Up)	P<0.05	–	31 pairs of OC and ANCs	A2780, OAW42, OVCAR4, SKOV3, HeyA8, IOSE-386, SKOV3/PTX, HeyA8/PTX	miR-654-5p, SIK2	–	UCA1 could promote the progression of paclitaxel resistance in OC by regulating the miR-654-5p/SIK2 axis.	[118]
OC	SDHAP1 (Up)	P<0.001	–	PTX-sensitive (n = 28) and PTX-resistant (n = 22) patients	SKOV3, Hey-8, SKOV3/PTX, Hey-8/PTX	miR-4465, Caspase 3/7, EIF4G2	–	SDHAP1 by regulating EIF4G2 expression *via* miR-4465 could confer paclitaxel resistance of OC.	[119]
OC	TUG1 (Up)	P<0.05	Female BALB/c athymic nude mouse	OC (N = 41) and benign ovarian tumor samples (N = 26)	A2780, IOSE80 and IOSE386, HEK293, SKOV3, A2780/R	LC3B-I/II, Caspase-3/7, Beclin-1, miR-29b-3p	–	Knockdown of TUG1 by sponging miR-29b-3p could decrease chemoresistance and the autophagic response in OC cells.	[120]
OC	HOTAIR (Up)	P<0.05	Female BALB/c-nu mouse	GEO, EGA, and TCGA databases	SKOV3, ES2, A2780, CAOV3, HCT-15	CHEK1, P-gp	–	HOTAIR by regulating CHEK1 could promote paclitaxel resistance in OC. knockdown of HOTAIR by promoting the G2/M phase could restore the sensitivity of cells to paclitaxel.	[121]
OC	KB-1471A8.2 (Down)	P<0.05	–	Normal ovarian (n = 10) and serous ovarian cancer tissue samples (n = 9)	A2780, SKOV3, A2780/Taxol, SKOV3/Taxol	DEPTOR, LC3B, CDC25C, PLK1, PTTG1, ESPL1, CCNA1, CCNB1, CCND1, CCNE1, CDK1, CDK2, CDK4, CDKN1A, CDKN1B	–	Overexpression of KB-1471A8.2 could increase the G0/G1 phase cell ratio and decreased the S phase cell ratio; therefore, it could suppress cell migration and proliferation and antagonize the paclitaxel resistance of OC cells.	[122]
OC	FER1L4 (Down)	P<0.01	–	–	IOSE80, HOSEpiC, OVCAR-3, Caov-3, SKOV3, SKOV3-PR	–	ERK, MAPK	Overexpression of FER1L4 *via* regulating the MAPK signaling pathway could inhibit paclitaxel tolerance of OC cells.	[39]
OC	SNHG5 (Down)	P<0.001	BALB/c nude mouse	36 pairs of OC and ANCs	SKOV3, MeyA-8, SKOV3/PTX, MeyA-8/PTX	miR-23a	–	Overexpression of SNHG5 by targeting miR-23a could improve the sensitivity of OC cells to PTX.	[35]
Cervical Cancer (CC)	LINC00511 (Up)	P<0.05	–	84 pairs of CC and ANCs	Hela, Hela/PTX	MMP-2, MMP-9, Caspase-3 Bcl-2, Bax, MRP1, P-gp	–	Knockdown of LINC00511 could prevent CC cell proliferation by reducing resistance to paclitaxel.	[115]
Cervical Cancer (CC)	RP11-381N20.2 (Down)	P<0.05	–	TCGA database	SiHa	Atg7, LC3A/B-II	–	Paclitaxel by inhibiting autophagy *via* lncRNARP11-381N20.2 could decrease the cell progression in CC.	[123]
Endometrial Cancer (EC)	CDKN2B-AS (Up)	P<0.01	–	EC patients: sensitive (n = 36) and insensitive (n = 51)	HEC-251, Ishikawa, HEC-1A, 293 T, Ishikawa/PA, HEC1A/PA	miR-125a-5p, Bcl-2, MRP4	–	Knockdown of CDKN2B-AS through the miR-125a-5p-Bcl2/MRP4 pathway could inhibit paclitaxel resistance in EC patients.	[124]

(*continued on next page*)

Table 9 (*continued*)

Type of Cancer	lncRNAs & Expression Pattern	P Value	Animal	Clinical Samples (Human)	Cell Lines	Target	Pathway	Observation	Ref
EC	HEIH (Up)	P<0.01	–	45 pairs of EC and ANCs	Ishikawa, HHUA, hESC, Ishikawa-RE, HHUA-RE	p38, c-Fos, C-Jun, AKT1	MAPK	Overexpression of HEIH by activating the MAPK pathway could promote the chemoresistance of EC cells.	[125]

Table 10
Role of lncRNAs in the modulation of response of head and neck cancers to paclitaxel.

Type of Cancer	lncRNAs & Expression Pattern	P Value	Animal	Clinical Samples (Human)	Cell Lines	Target	Pathway	Observation	Ref
Nasopharyngeal Carcinoma (NPC)	n375709 (Up)	P<0.05	–	–	CNE-2,5-8F, 6-10B, CNE-2-Pr	–	–	n375709 could be involved in the regulation paclitaxel resistance in NPC cells.	[127]
NPC	CCAT1 (Up)	P<0.001	BALB/c (nu/nu) mice	15 paclitaxel sensitive and 16 paclitaxel resistant patients	CNE1, CNE2, CNE1-PTX, CNE2-PTX	CPEB2, miR-181a	–	Knockdown of CCAT1 *via* the miR-181a/CPEB2 axis could enhance the sensitivity of paclitaxel in NPC cells.	[126]
NPC	H19 (Up)	P<0.05	BALA/C nude mouse	–	NP69, HNE3, C666-1, 5-8 F, SUNE1, 6-10B, C666-1/Taxol, 6-10B/ Adriamycin	P-gp, MRP1	–	Knockdown of H19 combined with paclitaxel could inhibit NPC progression.	[128]

Application of CRISPR/Cas9 system presents an effective procedure for development of novel model systems for the targeted alteration of endogenous loci, and this cutting-edge genome-editing tool can be altered to permit creation of more alterations to adjust gene expression beyond simple gene knockdown. Related methods are gene manipulation to suppress chemoresistance drugs, screening, recognition of different resistance molecular targets, and altering membrane transport proteins to enhancing drug delivery [21,157–159]. The main dysregulation of signaling cascades in paclitaxel resistance is related to Wnt/β-catenin, PI3 K/AKT/mTOR, HER2, HER3, MAPK/ERK, NF-κB, TGF-β, and PTEN/AKT pathways [16,18,75,148,160–163]. In order to figure out the efficacy of miR-195 expression on the response of NSCLC cells to MTAs in paclitaxel resistance, Ye et al. knocked out miR-195 utilizing CRISPR/Cas9 with pair of sgRNAs designed against the miR-195 locus. Therefore, by applying this gene-editing tool, they discovered that miR-195 with paclitaxel and eribulin could suppress the expression level of CHEK1, and thereby blocking the growth of cancer cells in NSCLC and contributing to sensitize to MTAs [28]. In addition, another research demonstrated ectopic expression for miR-421 results in paclitaxel resistance in NSCLC. In order to identify the upstream regulator of miR-421, one of the targets gene, β-catenin, was knocked out through the CRISPR/Cas9 procedure in NSCLC cells. Blocking the expression of miR-421 *via* AMO could promote ROS levels and the expression level of KEAP1, and thereby enhancing paclitaxel sensitivity in NSCLC and reducing cell proliferation, invasion, and migration significantly [20]. Therefore, the CRISPR/Cas9 system has been offered as a remedial method to reduce drug resistance in different paclitaxel-resistant cancers. This engineered genome-editing strategy includes two components: a guide RNA (gRNA or sgRNA) and a CRISPR-associated endonuclease (Cas protein). The gRNA is a short synthetic RNA produced of a scaffold sequence essential for Cas-binding and a user-defined ~20 nucleotide spacer that facilitates the genomic target to be altered [164,165]. Cas9-mediated HDR could create an accurate recombination event between a homologous DNA donor template and the impaired DNA region, leading to a precise modification of the double-strand breakage. Thus, HDR can be applied to offer specific correction or transgenes into the genome [166,167]. In order to eliminate the effect of antigen-specific T-cells directed against Cas9 protein and suppress the immune reaction with the aim of enhancing the chance of appropriate delivery of the CRISPR-Cas9 system, exosome-mimetic nanoplatforms, lipopolymer or viral vectors can be used to encapsulate this gene-editing tool that can promote the sensitivity of tumor cells to chemotherapy [168–171]. Therefore, the CRISPR/Cas9 system is a innovative gene editing method that can revert drug resistance due to secondary genomic mutations to a minimal level in resistance to anti-cancer drugs with an exact sgRNAs design and effective delivery. Fig. 3 depicts knocking out of tak1 gene through CRISPR/Cas9 system in order to improve paclitaxel sensitivity in tumor cells that can lead to decreasing phospho-JNK and PARP cleavage levels, and thereby triggering cell death *via* the activation of TAK1–JNK signaling pathway [172]. Additionally, a summary of clinical researches in order to detect the role of various genes causing paclitaxel resistance in different human cancer cells *via* CRISPR/Cas9 system is demonstrated in Table 16.

5. Paclitaxel nano-delivery systems leading towards promoting therapeutic applications in different human cancers

Nanoparticle delivery systems has recently drawn attention, particularly with the aim of improving patient outcomes in various types of cancer remedies. As an efficient chemotherapeutic factor, *via* encapsulating paclitaxel in different nano-delivery systems it can play an important role in promoting the standard-of-care remedy in variety of cancer cells [191,192]. One of the significant factor due to enhancing paclitaxel efficiency by packaging *via* nano-delivery systems based on polymers or lipids can increase the aqueous solubility of this drug remarkably and as a consequence elevate response to treatment. In addition, another valuable characteristic of these delivery systems that can take into consideration is their small size leading to promoting permeability and retention (EPR) effect of molecules of certain sizes typically liposomes, and nanoparticles in targeting cells. Importantly, this type of encapsulating paclitaxel can provide an opportunity to not be recognized *via* the recognition of reticuloendothelial system (RES) which can attenuate the side effects of our target drug in non- cancerous tissues. Therefore, higher maximum tolerated doses (MTD) of nanoparticles has become possible. High stability, high carrier capacity can also be considered as another significant technological advantages of these nanoparticles. [193–195]. Schmid et al. have detected that atezolizumab–nab-paclitaxel in patients with PD-L1–positive tumors in

Table 11
Role of lncRNAs in the modulation of response of breast cancer to paclitaxel (ANCs: adjacent normal controls).

Type of Cancer	lncRNAs & Expression Pattern	P Value	Animal	Clinical Samples (Human)	Cell Lines	Target	Pathway	Observation	Ref
Triple-Negative Breast Cancer (TNBC)	H19 (Up)	P<0.05	Male BALB/c nude mouse	–	MDA-MB-453, MDA-MB-157, MDA-MB-231, Hs578Bst, MCF-10A, MDA-MB-231/PTX	Bax, Bcl-2, Caspase-3	Akt	Knockdown of H19 *via* regulating the Akt pathway and triggering apoptosis could restore chemosensitivity in paclitaxel-resistant TNBC cells.	[107]
Triple-Negative Breast Cancer (TNBC)	LINC-PINT (Down)	P<0.05	–	GEPIA database	MDA-MB-231, BT-20, MDA-MB-231/PTX, BT-20/PTX	NONO	–	LINC-PINT *via* targeting the RNA-binding protein NONO could attenuate paclitaxel resistance in TNBC cells.	[130]
Breast Cancer (BCa)	FTH1P3 (Up)	P<0.01	Male BALB/c nude mouse	Mouse	MCF-7, MDA-MB-231, MDA-MB-468, MDA-MB-453, MCF-10A, MCF-7/PTX, MDAMB-231/PTX	miR-206, ABCB1,	–	Knockdown of FTH1P3 *via* the miR-206/ABCB1 axis could suppress the tumor growth of paclitaxel-resistant BCa cells.	[131]
BCa	MAPT-AS1 (Up)	P<0.05	Female nude mouse	TCGA database, 23 pairs of BCa and ANCs	MDA-MB-231, MDA-MB-468, MDA-MB-436	MAPT	–	Knockdown of MAPT-AS1 by regulating MAPT expression could sensitize cancer cells to paclitaxel and inhibit proliferation and migration in ER-negative BCa.	[132]
BCa	LINC00511 (Up)	P<0.0001	–	21 pairs of BCa and ANCs, TCGA dataset	MDA-MB-231, MCF-7, Hs-578 T, T47D, MCF-10A	miR-29c, CDK6	–	Knockdown of LINC00511 *via* regulating the miR-29c/CDK6 axis could enhance paclitaxel cytotoxicity in BCa.	[129]
BCa	CASC2 (Up)	P<0.05	Male BALB/c nude mouse	Paclitaxel sensitive (n = 17), paclitaxel-resistant (n = 17) tissues	MCF-7, MDA-MB-231, MCF-10A, MCF-7/PTX, MDAMB-231/PTX	miR-18a-5p, CDK19	–	CASC2 by regulating the miR-18a-5p/CDK19 could promote paclitaxel resistance in BCa.	[133]
BCa	UCA1 (Up)	P<0.05	BALB/c nude mouse	Paclitaxel sensitive (n = 30), paclitaxel-resistant (n = 30) tissues	MCF-7, MCF-10A, MCF-7/PTX	miR-613, CDK12	–	UCA1 *via* the miR-613/CDK12 axis could modulate paclitaxel resistance in BCa.	[134]
BCa	LINC00160 (Up)	P<0.01	BALB/c mice	47 pairs of BCa and ANCs	MCF10A, MCF-7, BT474, MCF-7/Tax	TFF3, Vimentin, E-cadherin, TF-C/EBPβ	–	LINC00160 by regulating TFF3 *via* the transcription factor C/EBPβ could mediate paclitaxel resistance in BCa cells.	[135]
BCa	NONHSAT141924 (Up)	P<0.01	–	35 pairs of BCa and ANCs	BT-549, MDA-MB-231, Hs-578 T, ZR-75-30, T-47D MCF-7,	p-CREB, Bcl-2, ABCB1, BCRP, E-cadherin, N-cadherin	–	NONHSAT141924 *via* the p-CREB/Bcl-2 apoptosis signaling pathway could promote paclitaxel chemotherapy resistance in BCa.	[125]
BCa	AC073284.4 (Down)	p<0.01		35 pairs of BCa and ANCs	MCF-7, SKBR3, MCF-7/PR, SKBR3/PR	miR-18b-5p, DOCK4, Snail, E-cadherin, Slug	–	Overexpression of AC073284.4 *via* the miR-18b-5p/DOCK4 axis could inhibit invasion, metastasis, and EMT in BCa cells.	[136]

triple-negative breast cancer accompanied with the desirable level of immunotherapy effectiveness among patients in both the intention-to-treat population and the PD-L1–positive subgroup. Therefore, nanoparticle albumin-bound (nab)–paclitaxel can plan an effective role in anticancer activity of chemotherapeutic drugs [196]. Another research have noted that, paclitaxel-loaded PBCA nanoparticles could eliminate multidrug resistance and promote the level of cytotoxicity to a large extent in ovarian cancer cells *via* suppressing P-gp activity creating through the nanoparticles system. Therefore, it can provide a promising mechanism to enhance nanoparticles efficacy and make them applicable procedure to lead drug delivery [197]. In addition, Zou et al. have demonstrated that a dual-drugs co-delivery nano-sized system contained by the dendrimer-derivative PEG-PAMAM copolymer with PTX and BNL co-loaded could be considered as an effective method to restrain multiple drug resistance in ovarian cancer cells which in turn could lead to more cytotoxicity and apoptosis, and increasing tumor cell growth suppression. As a consequence, PEG-PAMAM NPs could provide evidence of attenuating MDR in tumor cells after exposure to a chemotherapeutic agent including paclitaxel and Borneol and improving therapeutic efficacy as well [198]. Another study have discovered that multiblock HPMA copolymer-GEM and HPMA copolymer-PTX conjugates by transferring them as a combination of single factors that can provide a helpful procedure in order to remedy ovarian cancer [199]. Yin et al. have illustrated that R8-dGR peptide modified PTX and HCQ

Table 12
Role of lncRNAs in the modulation of response of GI cancers to paclitaxel (ANCs: adjacent normal controls).

Type of Cancer	lncRNAs & Expression Pattern	P Value	Animal	Clinical Samples (Human)	Cell Lines	Target	Pathway	Observation	Ref
Gastric Cancer (GC)	HOTAIR (Up)	P<0.01	–	30 pairs of GC and ANCs	BGC-823, SGC-7901, KATO-3, MGC-803, GES-1	miR-217, Cyclin-D1, GPC5, PTPN14	–	Overexpression of HOTAIR by targeting miR-217 could increase GC cell proliferation, cell cycle, and migration and promote drug resistance in GC.	[137]
Hepatocellular Carcinoma (HCC)	HOTAIR (Up)	P<0.05	–	–	HepG2, SMMC-7721, HepG2/Taxol, SMMC7721/Taxol	miR-34a, Bax, Bcl-2, Caspase-3	Wnt/ β-catenin, AKT	Knockdown of HOTAIR *via* accommodating Akt phosphorylation and Wnt/ β-catenin signaling by interacting with miR-34a could impair Taxol-resistance in HCC.	[138]
Esophageal Cancer (EC)	DDX11-AS1 (Up)	P<0.05	BALB/c nude mouse	82 pairs of ECa and ANCs	293 T, EC109, KYSE150, EC109/PTX	Sox2, Oct4, TOP2A, β-catenin, Histone-H3		Knockdown of DDX11-AS1 by inhibiting the TAF1/TOP2A axis could reduce the resistance of EC cells to paclitaxel.	[129]
Colorectal Cancer (CRC)	CRNDE (Up)	P<0.05	–	41 pairs of CRC and ANCs	NCM460, Caco-2, HT29, HCT15, SW480, SW620, Caco-2/PTX, HT29/PTX, HCT15/ PTX, SW480/PTX, SW620/PTX	miR-126-5p, ATAD2	–	CRNDE by regulating the miR-126-5p/ATAD2 axis could promote CRC cell progression and paclitaxel resistance.	[139]

Table 13
Role of lncRNAs in the modulation of response of prostate cancer to paclitaxel (ANCs: adjacent normal controls).

lncRNA	P Value	Animal	Clinical Samples (Human)	Cell Lines	Target	Pathway	Observation	Ref
DANCR	P<0.05	–	36 pairs of PCa and ANCs	PC3, C4-2, DU145, RWPE-1	miR-135a, Ki-67, PCNA, Caspase-3, Bax		Knockdown of DANCR by sponging miR-135a could increase paclitaxel sensitivity in PCa cells.	[140]
Linc00518	P<0.05	–	45 PCa and 10 ANCs	WPE-1, LNCap, DU145, PC3, DU145/PR, PC3/ PR	miR-216b-5p, GATA6		Overexpression of Linc00518 *via* sequestering miR-216b-5p could contribute to the paclitaxel resistance in PCa.	[141]
SNHG6	P<0.001	Male BALB/c nude mouse	63 pairs of PCa and ANCs	PC3, DU145, DU145/R, PC3/R	miR-186, Cyclin-D1, MMP9, Vimentin, E-cadherin, Caspase-3/9, MRP1, MDR1, ZEB1, Snail	–	Knockdown of SNHG6 by sponging miR-186 could elevate the sensitivity of PTX-resistant PCa cells to PTX.	[108]
CCAT1	P<0.05	–	30 pairs of PCa and ANCs	RWPE-1, PC3, DU145, PC3/ TXR, DU145/TXR	miR-24-3p, FSCN1, S6K, Bcl-2, PTEN, BCL-XL, MCL-1	AKT/ mTOR, ERK1/2	Knockdown of CCAT1 *via* regulation the miR-24-3p/FSCN1 axis could enhance the sensitivity of paclitaxel in PCa.	[134]

Table 14
Role of lncRNAs in the modulation of response of other cancers to paclitaxel (ANCs: adjacent normal controls).

Type of Cancer	lncRNAs & Expression Pattern	P Value	Animal	Clinical Samples	Cell Lines	Target	Pathway	Observation	Ref
Osteosarcoma (OS)	MA-linc1 (Up)	P<0.05	–	–	U2OS, SAOS2, H1299, SAOS2-PXL	Purα, Caspase-3	–	MA-linc1, as a novel lncRNA regulator of the cell cycle, could sensitize cancer cells to paclitaxel.	[142]
OS	ADAMTS9-AS2 (Down)	P<0.001	–	65 pairs of OS and ANCs	143B, Saos-2, MG-63, HOS, os-732, U2-OS, hFOB1.19	PTEN, miR-130a-5p	PI3 K/ AKT	Overexpression of ADAMTS9-AS2 *via* the miR-130a-5p/PTEN/PI3 K/AKT axis could suppress cell proliferation and increase sensitivity to PTX in OS.	[143]
Renal Cell Carcinoma (RCC)	TCL6 (Down)	P<0.05	–	10 pairs of RCC and ANCs, TCGA and GEO datasets	HK-2, KC, OS-RC-2, ACHN, 786-O, Caki-1, 786-O/ PTX, Caki-1/PTX	miR-221	–	TCL6 *via* downregulating miR-221 could sensitize RCC cells to PTX.	[144]

co-loaded liposomes could be really beneficial in accumulating chemotherapeutic drugs in tumor cells providing antimetastatic activity with suppression of tumor cell proliferation in primary and metastatic melanoma both in vivo and in vitro [200]. Furthermore, in another research Zhong et al. have detected that PTX nanodrug co-administered with iRGD can be taken into account as an effective drug delivery candidate for the treatment of colorectal cancer by increasing the facilitation of tumor penetration, and promoting tumor accumulation and antitumor effects [201]. Additionally, another research discovered that by applying implantable rough PTX-PLGA-MS microspheres because of

Table 15
Prognostic value of paclitaxel-associated lncRNA in cancers (OS: overall survival, DFS: disease-free survival, RFS: relapse-free survival, LAD: lung adenocarcinoma, BCa: breast cancer, OC: ovarian cancer, PCa: prostate cancer, RCC: renal cell carcinoma, ANCs: adjacent normal controls).

Sample Number	Kaplan-Meier Analysis	Multivariate Cox Regression	Ref
76 pairs of LAD and ANCs	–	Higher expression of KCNQ1OT1 was associated with large tumors, poor differentiation, positive lymphatic metastasis, and TNM stages.	[110]
50 pairs of LAD and adjacent normal tissues	High level of ANRIL was associated with poorer OS and DFS rate.	Higher expression of ANRIL was associated with differentiation and TNM stage.	[112]
OC (N = 41) and benign ovarian tumor samples (N = 26)	High level of TUG1 was associated with poorer OS rate.	–	[120]
GEO, EGA, and TCGA databases	High level of HOTAIR was associated with poorer OS and rate.	–	[121]
84 pairs of CC and ANCs	High level of LINC00511 was associated with poorer OS and RFS rates.	Higher expression of LINC00511 was associated with tumor stage, tumor size, LNM and HPV16 infection.	[115]
EC patients including sensitive (n = 36) and insensitive (n = 51) groups	–	Higher expression of CDKN2B-AS was associated with high pathological grade.	[124]
23 pairs of BCa and ANCs	–	Higher expression of MAPT-AS1 was associated with metastatic lymph nodes and stages.	[132]
47 pairs of BCa and ANCs	High level of LINC00160 was associated with poorer OS rate.	–	[135]
30 pairs of GC and ANCs	–	Higher expression of HOTAIR was associated with late stage.	[137]
45 PCa and 10 ANCs	High level of Linc00518 was associated with poor OS rate.	–	[141]
82 pairs of EC and ANCs	High level of DDX11-AS1 was associated with poor OS rate.	The expression of TOP2A, DDX11-AS1, and TAF1 was associated with the prognosis of EC patients.	[129]
TCGA database	High level of RP11-381N20.2 was associated with poor OS rate.	Higher expression of RP11-381N20.2 was associated with TNM staging and tumor size.	[123]
36 pairs of OC and ANCs	High level of SNHG5 was associated with poor OS rate.	Higher expression of SNHG5 was associated with tumor grade, FIGO stage, and Lymph node metastasis.	[35]
56 pairs of LAD and ANCs	Low level of ENST00000500843 was associated with poorer OS and RFS rates.	Lower expression of ENST00000500843 was associated with tumor diameter, pathological differentiation, and metastasis of lymph nodes.	[113]
65 pairs of OS and ANCs	Low level of ADAMTS9-AS2 was associated with poorer OS rate.	Lower expression of ADAMTS9-AS2 was associated with larger tumor size, advanced enneking stage, poor histological differentiation, and distant metastasis.	[143]
10 pairs of RCC and ANCs, TCGA and GEO datasets	Low level of TCL6 was associated with poorer OS and DFS rates.	–	[144]

their particular morphology can have a helpful role in diminishing the limitations caused by paclitaxel containing excessive drug accumulation, uncontrolled drug release, tumor cells resistance to chemotherapeutic drugs and improvement of drug-loading capacity with the aim of enhancing response to therapy in glioma patients [202]. An Overview of various paclitaxel loaded polymeric and lipid-based nanoparticles is represented in Table 17.

6. Discussion

Paclitaxel is an extensively used chemotherapeutic agent in the treatment of human cancers. Emergence of resistance to this drug is regarded as a major problem in the clinical settings. Dysregulation of ncRNAs has been shown to be implicated in this problem. Consistent with the widespread use of paclitaxel in the treatment of patients with ovarian, breast or lung cancers, these types of cancers have been the mostly assessed malignancies in the terms of assessment of the role of ncRNAs in conferring resistance to paclitaxel. Wnt/β-catenin, AKT/ERK, PI3 K/AKT, mTOR, NF-κB and STAT related pathways are among the pathways which are involved in the process of modulation of paclitaxel sensitivity by ncRNAs. In addition, a number of paclitaxel-sensitizing herbal agents exert their effects through modulation of expression of ncRNAs. Therefore, ncRNAs are regarded as molecular targets for enhancement of the effects of herbal medicines as well.

The significant role of ncRNAs in conferring paclitaxel resistance/sensitivity has also been reflected by their remarkable impact on clinical outcome of patients with diverse types of cancers. As a rule, overexpression of miRNA/lncRNAs that enhance sensitivity of cancer cells to this drug is associated with higher survival of patients and vice versa.

7. Conclusion

LncRNAs and miRNAs interact with each other to modulate response of cancer cells to paclitaxel. Several lncRNA/miRNA axes have been identified to be functional in this regard. For instance, the SNHG5/ miR-23a and NEAT1/miR-194 axes in the ovarian cancer [35,114] and Linc00518/ miR-216b-5p axis in the prostate cancer [235] are among functional axes in the regulation of response of cancer cells to paclitaxel. These observations further highlight the importance of comprehensive assessment of expression pattern of different classes of ncRNAs for clarification of the molecular pathways in this cellular process.

Based on the remarkable roles of ncRNAs in altering response of cancer cells to paclitaxel, targeted therapies against these transcripts represent a putative treatment modality for combating resistance to this agent and enhancing survival of patients. The results of in vivo studies support the applicability of antisense oligodeoxyribonucleotide therapies in animal models. However, these modalities have not been examined in the clinical settings.

Ethics approval and consent to Participant

Not applicable.

Consent of publication

Not applicable.

Availability of data and materials

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

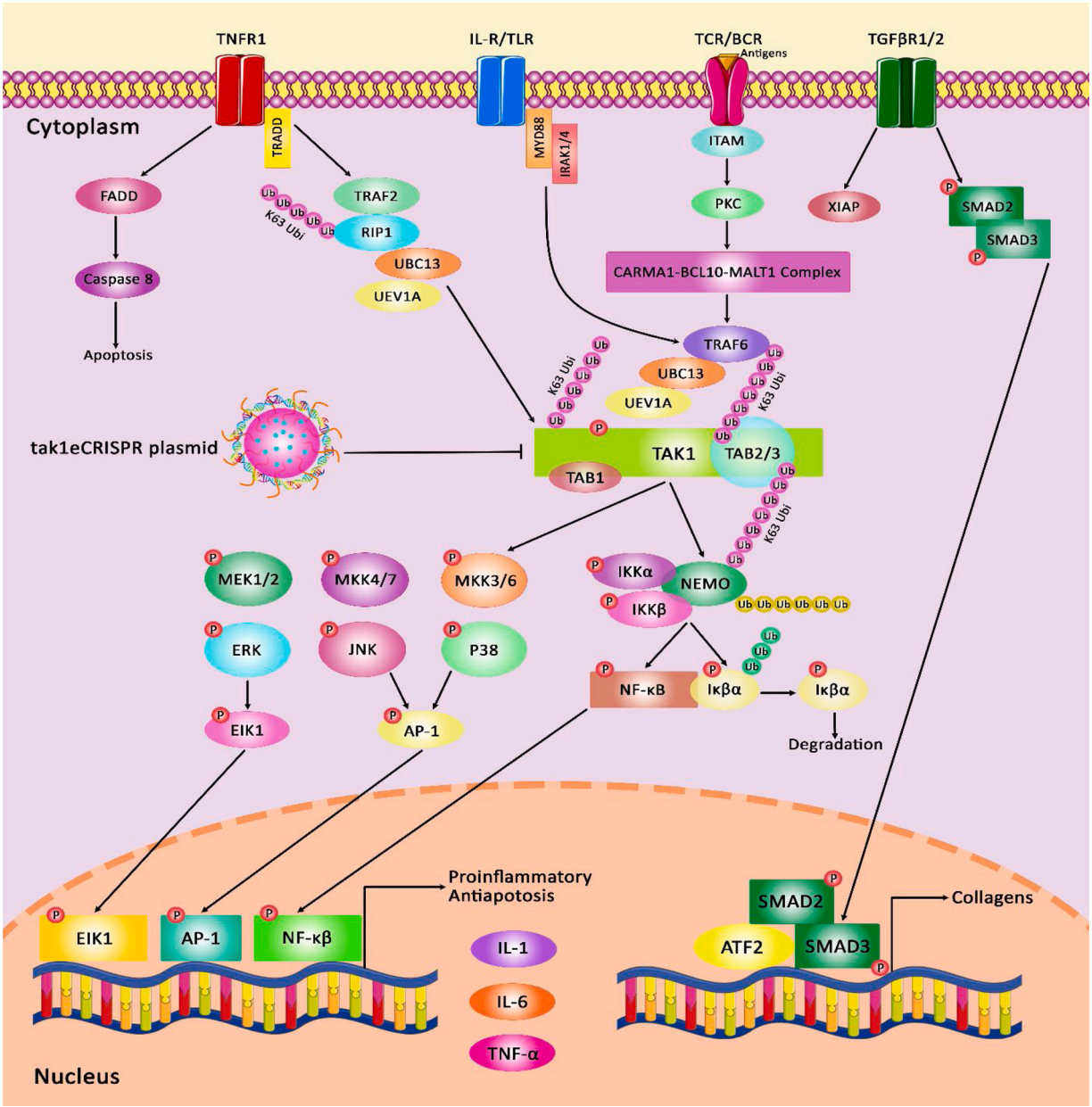

Fig. 3. A schematic diagram of tak1eCRISPR plasmid combined with PTX with the aim of editing TAK1 gene to attenuate paclitaxel resistance *via* the TAK1–JNK signaling pathway. TAK1 and TAB1 can have effective roles in triggering apoptotic process *via* NF- κB, JNK, ERK, and p38 signaling transduction cascades. Upregulation of TAK1 in tumor cells treated with CRISPR editing of the tak1 gene mutation accompanied with paclitaxel treatment could provide a remarkable evidence of enhancing cell death rate, PARP cleavage and phosphorylation of JNK. This cutting-edge gene editing tool *via* inserting a cytosine base and creating frameshift mutation in TAK1 gene could trigger cell apoptosis through the TAK1–JNK activation pathway, and thereby enhancing paclitaxel sensitivity in cancer cells. As a consequence, this can highlight the role of TAK1 gene in chemosensitivity of paclitaxel and other chemotherapeutic agents.

Table 16
Pre-clinical researches applying CRISPR/Cas9 to detect the role of various genes in response to chemotherapeutic options.

Cancer	Target	In vitro	Cell line	Animal	In vivo	CRISPR	Vector	Treatment	Effect	Ref
Pancreatic ductal adenocarcinoma (PDAC)	XPO1	+	HEK293, HEK293 XPO1^{C258S}	–	–	Editing (C528S mutant in exon 14)	Plasmid	Nab-paclitaxel, Gemcitabine, Selinexor (KPT-330)	Sensitized the cells	[173]
Triple-negative breast cancer (TNBC)	TMEPAI	+	BT-549	–	–	Editing (remove exon 4)	Plasmid	Paclitaxel, Doxorubicin	Sensitized the cells	[174]
Cervical carcinoma (CC)	miR-214	+	HeLa, C33A, CaSki	–	–	Knockout	Plasmid	Paclitaxel, Doxorubicin, Cisplatin	Sensitized the cells	[175]
CC	PPP1R7, PPP2R5B, PPP1R7, PPP1R11, ABCC9, IL37, EIF3C, AKT1S1	+	SiHa	–	–	Knockout screening	Lentiviral	Paclitaxel	Sensitized the cells	[176]
Ovarian cancer (OC)	BIRC5	+	SKOV3, OVCAR3	–	–	Editing (targeting exon 1)	Lentiviral	Paclitaxel	Sensitized the cells	[177]
OC	DNMT1	+	SKOV-3, SKOV-3eGFP+	4–6-week-old female BALB/c mice	+	Knockout	Plasmid	Paclitaxel	Sensitized the cells	[155]
OC	HE4	+	SKOV3, OVCAR8	–	–	Knockout	Plasmid	Paclitaxel, Cisplatin	Sensitized the cells	[178]
High-grade serous ovarian cancer (HGSOC)	BCL2L1, BCL2L1	+	Kuramochi, OVSAHO	–	–	Knockout	Lentiviral	Paclitaxel, Cisplatin	Sensitized the cells	[179]
Epithelial ovarian cancer (EOC)	KPNB1, ERBB2, RAF1	+	SKOV3	Female athymic nude mice	+	Loss-of-Function Screen	Lentiviral	Paclitaxel	Sensitized the cells	[180]
Osteosarcoma (OS)	PD-L1	+	KHOS, MNNG/HOS	–	–	Knockout (targeting exon 2 and 3)	Plasmid	Paclitaxel, Doxorubicin	Sensitized the cells	[181]
Non–small cell lung cancer (NSCLC)	RSF-1	+	H1299, H460	6-week-old female nude mice	+	Knockout	Plasmid	Paclitaxel	Sensitized the cells	[156]
NSCLC	β-catenin	+	A549	–	–	Knockout	Lentiviral	Paclitaxel	Sensitized the cells	[20]
NSCLC	Aurora-B	+	A549/CDDP, A549/PTX	–	–	Knockout	Plasmid	Paclitaxel, Cisplatin	Sensitized the cells	[182]
Colorectal cancer (CRC)	RBX2	+	HCT116, SW480	5-week-old BALB/c nude mice	+	Knockout	Plasmid	Paclitaxel	Sensitized the cells	[183]
Gastric cancer (GC)	AEP	+	SGC7901, MKN45	–	–	Knockout	Lentiviral	Paclitaxel, T-DM1, Docetaxel	Sensitized the cells	[184]
Esophageal squamous cell carcinoma (ESCC)	CDKN1A, TSPAN4, ELAVL2, JUNB, PAAF1	+	KYSE-180	–	–	Genome-wide CRISPR activation screening	Lentiviral	Paclitaxel	Sensitized the cells	[185]
Anaplastic thyroid carcinoma (ATC)	CDK7, PPP1R15A, PAX8, EGFR	+	CAL-62, 8505C	–	–	Knockout	Lentiviral	Paclitaxel, Doxorubicin	Sensitized the cells	[186]
–	TAK1	+	HEK293, 8305C	–	–	Editing (inserting a cytosine base, creating frameshift mutation)	Plasmid	Paclitaxel	Sensitized the cells	[172]
–	BCL-W	+	HeLa	–	–	Knockout	Plasmid	Paclitaxel	Sensitized the cells	[187]
–	ATG5	+	Ras-NIH 3T3, Ras-NIH 3T3/Mdr	–	–	Knockout (targeting exon 2)	Plasmid	Paclitaxel	Induced resistance	[188, 189]
–	Cdk5	–	–	6–8-week-old female BALB/c mice bearing B16F10 melanoma tumor	+	Knockout	Plasmid	Paclitaxel	Sensitized the cells	[190]

Table 17
An overview of PX-loaded Polymeric and Lipid nanoparticles.

Nanoparticle Delivery Systems	Compound	Types of Cancer	NP Preparation Technique	Nanocarrier Structures	Particle Size (nm)	Drug Encapsulation Efficiency (%)	In vitro	In vivo	Ref
PLGA	Polymeric	Glioblastoma	Emulsion solvent evaporation	PTX/SPIO-NPs	250 ± 20	30 ± 6	+	+	[203]
		Hepatocellular carcinoma	Emulsion solvent evaporation	PBAE/PLGA/PTX	126.9	70.8	+	+	[204]
		Non-small lung cancer	Emulsion solvent evaporation	PTX-FA-NPs	161.81 ± 6.97	71.71	+	+	[205]
		Breast cancer	Emulsion solvent evaporation	PTX-loaded CA-PLA-TPGS	112.9 ± 3.1	98.81	+	+	[206]
PLA	Polymeric	–	Emulsion solvent evaporation	PTX-m-NPs PTX-p-NPs	120.3 ± 1.1 90.4 ± 2.5	90.2 ± 4.0 90.9 ± 5.4	+	+	[207]
		–	Dialysis	PTX-PLA NPs PTX-MPEG-PLA NPs	441.9 179.5	20 18.3	+	–	[208]
		Breast cancer	Film hydration	PTX-loaded LDP2000, LPP2000, LPP5000	97.7 ± 4.0 119.1 ± 2.6 105.7 ± 5.6	51.5 ± 3.3 54.2 ± 0.9 62.8 ± 4.3	+	+	[209]
PCL	Polymeric	–	Nanoprecipitation Emulsion-solvent evaporation homogenized with an Ultra-Turrax Emulsion-solvent evaporation homogenized with an ultrasonicator	PTX-loaded PCL–TPGS NPs	261.6 ± 1.1 444.3 ± 21.7 237.8 ± 5.8	13.6 15.9 63	+	+	[210]
		–	Emulsion solvent evaporation	PTX-loaded (PGA-co-PCL)-b-TPGS2k NPs	202.1 ± 5.3	96.5	+	+	[211]
		–	Dialysis	PTX-loaded HA-PBCA NPs	291–325	90	+	–	[212]
PBCA	Polymeric	–	Emulsion solvent evaporation Miniemulsion	PTX-loaded PBCA	56.2 ± 2.0 99.7 ± 4.4	18.0 ± 2.0 56.6 ± 4.0	+	–	[213]
		Ovarian cancer	Interfacial polymerization	PTX-loaded PBCA	224.5 ± 5.7	99.23	+	–	[197]
		Bladder cancer	Emulsion solvent evaporation	PTX/HPG-C10-PEG	232	95	+	+	[214]
HPG	Polymeric	–	Nanoprecipitation	PTX-loaded HPG-g-CD1, HPG-g-CD2, HPG-g-CD3	225.2 ± 2.9 283.8 ± 4.1 305.5 ± 4.6	82.81 89.68 88.73	+	–	[215]
		Hepatocellular carcinoma	Dialysis	PTX-loaded HPG-g-CD, HPG-g-LA, Mixed NPs-4, FITC-mixed NPs-4	278.5 ± 4.243 166.6 ± 4.05 225.7 ± 5.232 220.4 ± 4.231	88.24 40.62 47.91 48.75	+	–	[216]
		–	Film formation	PTX-loaded PEG-PE micelles (M1, M2, M3, M4)	25.48 ± 0.23 18.97 ± 0.08 16.33 ± 0.37 16.31 ± 0.31	81.34 ± 11.46 78.9 ± 9.7 83.28 ± 2.52 86.5 ± 0.58	+	+	[217]
PEG-PE	Polymeric	Ovarian cancer	Film hydration	PCL-Loaded PEG2000-PE/vitamin E micelles	17.6 ± 1.7	90	+	+	[218]
		–	Film formation	PTX-PEG-PE PTX-PEG-PE/Vit. E (85:15) PTX-PEG-PE/Vit. E (95:5)	14.5 ± 3.5 23.1 ± 0.3 21.4 ± 0.2	58.0 ± 4.9 70.3 ± 3.0 96.6 ± 5.8	+	–	[219]
		–	Desolvation	PTX- loaded Albumin	210	95	+	–	[220]
Albumin	Polymeric	–	Dialysis	PTX-loaded OSA-0-micelles PTX-loaded OSA-2-micelles PTX-loaded OSA-4-micelles PTX-loaded OSA-6-micelles PTX-loaded OSA-8-micelles	171.8 ± 8.6 152.8 ± 4.9 147.4 ± 6.8 143.0 ± 3.4 123.2 ± 5.7	58.7 ± 5.6 81.8 ± 3.4 84.8 ± 2.4 85.8 ± 1.1 90.5 ± 2.9	+	–	[221]
		–	Emulsion solvent evaporation	PTX-loaded CS-g-PCL micelles	480	82	+	–	[222]
Chitosan	Polymeric	–	Emulsion solvent evaporation	PTX-loaded Chitosan/GMO	432.5 ± 37.1	98.9 ± 0.83	+	–	[223]
		–	Dialysis	PTX-loaded LMWSC-NPT	274.6 ± 68.8	70	–	+	[224]
		–	Film hydration	LEP-ETU	150	>90	+	–	[225]
Liposomes	Lipid	Triple-negative breast cancer	Film hydration Dialysis	PTX-Lip PTX-Fru-Lip PTX-RGD-Lip PTX-Fru-RGD-Lip	108.5 ± 4.7 108.8 ± 2.2 110.8 ± 6.2 112.0 ± 2.5	86.65 ± 1.53 81.47 ± 1.11 82.60 ± 2.09 82.16 ± 2.92	+	+	[226]

(*continued on next page*)

Table 17 (*continued*)

Nanoparticle Delivery Systems	Compound	Types of Cancer	NP Preparation Technique	Nanocarrier Structures	Particle Size (nm)	Drug Encapsulation Efficiency (%)	In vitro	In vivo	Ref
SLNs	Lipid	Breast cancer	Dialysis	PTX-(FrupRGD)-Lip	113.6 ± 2.1	80.42 ± 3.02	+	–	[227]
				LCFL-PTX/DXR	244.4 ± 28.1	74.1 ± 1.8			
		–	Emulsion solvent evaporation	PTX-Brij78-SLN	103.5 ± 29.2	58.262.5	+	+	[228]
			Dialysis	PTX-F68-SLN	220 ± 98	75.463.2			
		Gastric cancer	Solvent injection	PTX/17-AAG loaded SLNs	158.5 ± 70.2	90	+	+	[31]
		Breast cancer	High-pressure homogenization	PTX- SLNs	210.5 ± 86.3	–	+	–	[229]
		Non-small lung cancer	Nanoprecipitation Sonication	PTX/ERL-SLCN	121 ± 1.4	92.9 ± 1.1	+	–	[230]
Lipid Nanocapsules	Lipid	Glioblastoma	Phase inversion	PTX-loaded LNC	55.4 ± 1.5	98	+	–	[231]
				PTX-loaded LNC-SDS	53.1 ± 1.5	98			
				PTX-loaded CS-LNC	69.9 ± 3.4	98			
		–	Polymerization/emulsion	Fresh, paclitaxel-loaded LNC	53.4 ± 1.9	50–80	+	–	[232]
				Thawed, paclitaxel-loaded LNC	67.5 ± 0.5				
Micro- and Nano-Emulsions	Lipid	–	Ultrasonication	Paclitaxel nanoemulsion	139 ± 1.6	100	+	–	[233]
				Paclitaxel PEG-modified nanoemulsion	138 ± 1.6	100			
		–	Sonication	PTX-emulsion	150	>95	+	+	[234]

Funding

Not applicable.

Authors' contributions

MT and SGF supervised the study, wrote the draft and edited the submission. HSH, AA, SHAR and MP performed the data collection, designed the tables and figures. All of the authors are contributed equally and fully aware of submission.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgement

Not applicable.

References

[1] S.B. Horwitz, Taxol (paclitaxel): mechanisms of action, Ann. Oncol. 5 (Suppl. 6) (1994) S3–6.

[2] B.A. Weaver, How Taxol/paclitaxel kills cancer cells, Mol. Biol. Cell 25 (18) (2014) 2677–2681.

[3] P.B. Schiff, J. Fant, S.B. Horwitz, Promotion of microtubule assembly in vitro by taxol, Nature 277 (5698) (1979) 665–667.

[4] J.C. Waters, R.H. Chen, A.W. Murray, E.D. Salmon, Localization of Mad2 to kinetochores depends on microtubule attachment, not tension, J. Cell Biol. 141 (5) (1998) 1181–1191.

[5] J.J. Kim, B. Yin, C.S. Christudass, N. Terada, K. Rajagopalan, B. Fabry, D.Y. Lee, T. Shiraishi, R.H. Getzenberg, R.W. Veltri, S.S. An, S.M. Mooney, Acquisition of paclitaxel resistance is associated with a more aggressive and invasive phenotype in prostate cancer, J. Cell. Biochem. 114 (6) (2013) 1286–1293.

[6] R.Z. Yusuf, Z. Duan, D.E. Lamendola, R.T. Penson, M.V. Seiden, Paclitaxel resistance: molecular mechanisms and pharmacologic manipulation, Curr. Cancer Drug Targets 3 (1) (2003) 1–19.

[7] S.V. Ambudkar, C. Kimchi-Sarfaty, Z.E. Sauna, M.M. Gottesman, P-glycoprotein: from genomics to mechanism, Oncogene 22 (47) (2003) 7468–7485.

[8] Y. Huang, W. Sadée, Membrane transporters and channels in chemoresistance and-sensitivity of tumor cells, Cancer Lett. 239 (2) (2006) 168–182.

[9] J.T. Lee, L.S. Steelman, J.A. McCubrey, Phosphatidylinositol 3′-kinase activation leads to multidrug resistance protein-1 expression and subsequent chemoresistance in advanced prostate cancer cells, Cancer Res. 64 (22) (2004) 8397–8404.

[10] P. Giannakakou, D.L. Sackett, Y.-K. Kang, Z. Zhan, J.T. Buters, T. Fojo, M. S. Poruchynsky, Paclitaxel-resistant human ovarian cancer cells have mutant β-tubulins that exhibit impaired paclitaxel-driven polymerization, J. Biol. Chem. 272 (27) (1997) 17118–17125.

[11] D. Aoki, Y. Oda, S. Hattori, K.-i. Taguchi, Y. Ohishi, Y. Basaki, S. Oie, N. Suzuki, S. Kono, M. Tsuneyoshi, Overexpression of class III β-tubulin predicts good response to taxane-based chemotherapy in ovarian clear cell adenocarcinoma, Clin. Cancer Res. 15 (4) (2009) 1473–1480.

[12] X. Tian, H. Zhang, B. Zhang, J. Zhao, T. Li, Y. Zhao, Microarray expression profile of long non-coding RNAs in paclitaxel-resistant human lung adenocarcinoma cells, Oncol. Rep. 38 (1) (2017) 293–300.

[13] D.P. Bartel, MicroRNAs: genomics, biogenesis, mechanism, and function, Cell 116 (2) (2004) 281–297.

[14] Y. Cai, X. Yu, S. Hu, J. Yu, A brief review on the mechanisms of miRNA regulation, Genomics Proteomics Bioinform. 7 (4) (2009) 147–154.

[15] N. Chen, H.S. Chon, Y. Xiong, D.C. Marchion, P.L. Judson, A. Hakam, J. Gonzalez-Bosquet, J. Permuth-Wey, R.M. Wenham, S.M. Apte, Human cancer cell line microRNAs associated with in vitro sensitivity to paclitaxel, Oncol. Rep. 31 (1) (2014) 376–383.

[16] C. Ma, X. Shi, W. Guo, J. Niu, G. Wang, miR-107 enhances the sensitivity of breast cancer cells to paclitaxel, Open Med. 14 (1) (2019) 456–466.

[17] M. Liu, H. Xiusheng, X. Xiao, Y. Wang, Overexpression of miR-422a inhibits cell proliferation and invasion, and enhances chemosensitivity in osteosarcoma cells, Oncol. Rep. 36 (6) (2016) 3371–3378.

[18] K. Zhao, X. Li, X. Chen, Q. Zhu, F. Yin, Q. Ruan, J. Xia, Z. Niu, Inhibition of miR-140-3p or miR-155-5p by antagomir treatment sensitize chordoma cells to chemotherapy drug treatment by increasing PTEN expression, Eur. J. Pharmacol. 854 (2019) 298–306.

[19] B. Peng, C. Li, P. Cai, L. Yu, B. Zhao, G. Chen, Knockdown of miR-935 increases paclitaxel sensitivity via regulation of SOX7 in non-small-cell lung cancer, Mol. Med. Rep. 18 (3) (2018) 3397–3402.

[20] F.-G. Duan, M.-F. Wang, Y.-B. Cao, D. Li, R.-Z. Li, X.-X. Fan, I. Khan, H.-L. Lai, Y.-Z. Zhang, W.W.-L. Hsiao, MicroRNA-421 confers paclitaxel resistance by binding to the KEAP1 3′ UTR and predicts poor survival in non-small cell lung cancer, Cell Death Dis. 10 (11) (2019) 1–14.

[21] Y. Lu, J. Wang, L. Liu, L. Yu, N. Zhao, X. Zhou, X. Lu, Curcumin increases the sensitivity of Paclitaxel-resistant NSCLC cells to Paclitaxel through microRNA-30c-mediated MTA1 reduction, Tumour Biol. 39 (4) (2017), 1010428317698353.

[22] H. Sun, X. Zhou, Y. Bao, G. Xiong, Y. Cui, H. Zhou, Involvement of miR-4262 in paclitaxel resistance through the regulation of PTEN in non-small cell lung cancer, Open Biol. 9 (7) (2019), 180227.

[23] C.-C. Sun, S.-J. Li, F. Zhang, Y.-D. Zhang, Z.-Y. Zuo, Y.-Y. Xi, L. Wang, D.-J. Li, The novel miR-9600 suppresses tumor progression and promotes paclitaxel sensitivity in non–small-cell lung cancer through altering STAT3 expression, Mol. Ther. Nucleic Acids 5 (2016) e387.

[24] C. Lu, Z. Xie, Q. Peng, MiRNA-107 enhances chemosensitivity to paclitaxel by targeting antiapoptotic factor Bcl-w in non small cell lung cancer, Am. J. Cancer Res. 7 (9) (2017) 1863.

[25] K. Chen, W. Shi, Autophagy regulates resistance of non-small cell lung cancer cells to paclitaxel, Tumor Biol. 37 (8) (2016) 10539–10544.

[26] C.-M. Su, M. Wang, C. Hong, H.-A. Chen, Y.-H. Su, C.-H. Wu, M.-T. Huang, Y. W. Chang, S.S. Jiang, S.-Y. Sung, miR-520h is crucial for DAPK2 regulation and breast cancer progression, Oncogene 35 (9) (2016) 1134–1142.
[27] S. Wang, L. Zhu, W. Zuo, Z. Zeng, L. Huang, F. Lin, R. Lin, J. Wang, J. Lu, Q. Wang, MicroRNA-mediated epigenetic targeting of Survivin significantly enhances the antitumor activity of paclitaxel against non-small cell lung cancer, Oncotarget 7 (25) (2016) 37693.
[28] X. Yu, Y. Zhang, X. Ma, A. Pertsemlidis, miR-195 potentiates the efficacy of microtubule-targeting agents in non-small cell lung cancer, Cancer Lett. 427 (2018) 85–93.
[29] J. Ye, Z. Zhang, L. Sun, Y. Fang, X. Xu, G. Zhou, miR-186 regulates chemo-sensitivity to paclitaxel via targeting MAPT in non-small cell lung cancer (NSCLC), Mol. Biosyst. 12 (11) (2016) 3417–3424.
[30] X. Xu, S. Jin, Y. Ma, Z. Fan, Z. Yan, W. Li, Q. Song, W. You, Z. Lyu, Y. Song, miR-30a-5p enhances paclitaxel sensitivity in non-small cell lung cancer through targeting BCL-2 expression, J. Mol. Med. 95 (8) (2017) 861–871.
[31] Y.-f. Zhao, M.-l. Han, Y.-j. Xiong, L. Wang, Y. Fei, X. Shen, Y. Zhu, Z.-q. Liang, A miRNA-200c/cathepsin L feedback loop determines paclitaxel resistance in human lung cancer A549 cells in vitro through regulating epithelial–mesenchymal transition, Acta Pharmacol. Sin. 39 (6) (2018) 1034–1047.
[32] H. Koh, H. Park, N. Chandimali, D.L. Huynh, J.J. Zhang, M. Ghosh, M. Gera, N. Kim, Y. Bak, D.-Y. Yoon, MicroRNA-128 suppresses paclitaxel-resistant lung cancer by inhibiting MUC1-C and BMI-1 in cancer stem cells, Oncotarget 8 (66) (2017), 110540.
[33] L. Li, Q. Xu, Y. Dong, G. Li, L. Yang, L. Wang, H.Y. Li, MiR-181a upregulation is associated with epithelial-to-mesenchymal transition (EMT) and multidrug resistance (MDR) of ovarian cancer cells, Eur. Rev. Med. Pharmacol. Sci. 20 (10) (2016) 2004–2010.
[34] G. Du, D. Cao, L. Meng, miR-21 inhibitor suppresses cell proliferation and colony formation through regulating the PTEN/AKT pathway and improves paclitaxel sensitivity in cervical cancer cells, Mol. Med. Rep. 15 (5) (2017) 2713–2719.
[35] H. Lin, L. Shen, Q. Lin, C. Dong, B. Maswela, G.S. Illahi, X. Wu, SNHG5 enhances Paclitaxel sensitivity of ovarian cancer cells through sponging miR-23a, Biomed. Pharmacother. 123 (2020), 109711.
[36] L. Feng, F. Shen, J. Zhou, Y. Li, R. Jiang, Y. Chen, Hypoxia-induced up-regulation of miR-27a promotes paclitaxel resistance in ovarian cancer, Biosci. Rep. 40 (4) (2020).
[37] Y. Zhou, M. Wang, T. Shuang, Y. Liu, Y. Zhang, C. Shi, MiR-1307 influences the chemotherapeutic sensitivity in ovarian cancer cells through the regulation of the CIC transcriptional repressor, Pathol.-Res. Pract. 215 (10) (2019), 152606.
[38] S. Zhang, J. Cheng, C. Quan, H. Wen, Z. Feng, Q. Hu, J. Zhu, Y. Huang, X. Wu, circCELSR1 (hsa_circ_0063809) contributes to paclitaxel resistance of ovarian cancer cells by regulating FOXR2 expression via miR-1252, Mol. Ther. Nucleic Acids 19 (2020) 718–730.
[39] J. Jiang, C. Xie, Y. Liu, Q. Shi, Y.J.B. Chen, Up-regulation of miR-383-5p suppresses proliferation and enhances chemosensitivity in ovarian cancer cells by targeting TRIM27, Pharmacotherapy 109 (2019) 595–601.
[40] X. Bing, Z. Zhao, Y. Wu, Y. Wang, Y. Zhao, J. Wang, Circular RNA circTNPO3 regulates paclitaxel resistance of ovarian cancer cells by miR-1299/NEK2 signaling pathway, Mol. Therapy Nucleic Acids (2020).
[41] X. Cui, Y. Sun, M. Shen, K. Song, X. Yin, W. Di, Y. Duan, Enhanced chemotherapeutic efficacy of paclitaxel nanoparticles co-delivered with microRNA-7 by inhibiting paclitaxel-induced EGFR/ERK pathway activation for ovarian cancer therapy, ACS Appl. Mater. Interfaces 10 (9) (2018) 7821–7831.
[42] J.-Y. Jeong, H. Kang, T.H. Kim, G. Kim, J.-H. Heo, A.-Y. Kwon, S. Kim, S.-g. Jung, H.-J. An, MicroRNA-136 inhibits cancer stem cell activity and enhances the anti-tumor effect of paclitaxel against chemoresistant ovarian cancer cells by targeting Notch3, Cancer Lett. 386 (2017) 168–178.
[43] C.L.A. Yeung, N.-N. Co, T. Tsuruga, T.-L. Yeung, S.-Y. Kwan, C.S. Leung, Y. Li, E. S. Lu, K. Kwan, K.-K. Wong, Exosomal transfer of stroma-derived miR21 confers paclitaxel resistance in ovarian cancer cells through targeting APAF1, Nat. Commun. 7 (1) (2016) 1–14.
[44] T.H. Kim, J.-Y. Jeong, J.-Y. Park, S.-W. Kim, J.H. Heo, H. Kang, G. Kim, H.J. An, miR-150 enhances apoptotic and anti-tumor effects of paclitaxel in paclitaxel-resistant ovarian cancer cells by targeting Notch3, Oncotarget 8 (42) (2017) 72788.
[45] J. Zhang, J. Qin, Y. Su, miR-193b-3p possesses anti-tumor activity in ovarian carcinoma cells by targeting p21-activated kinase 3, Biomed. Pharmacother. 96 (2017) 1275–1282.
[46] K. Nakamura, K. Sawada, M. Miyamoto, Y. Kinose, A. Yoshimura, K. Ishida, M. Kobayashi, A. Shimizu, E. Nakatsuka, K. Hashimoto, Downregulation of miR-194-5p induces paclitaxel resistance in ovarian cancer cells by altering MDM2 expression, Oncotarget 10 (6) (2019) 673.
[47] Y. Cui, K.e. She, D. Tian, P. Zhang, X. Xin, miR-146a inhibits proliferation and enhances chemosensitivity in epithelial ovarian cancer via reduction of SOD2, Oncol. Res. 23 (6) (2016) 275–282.
[48] C. Shi, M. Wang, LINC01118 modulates paclitaxel resistance of epithelial ovarian cancer by regulating miR-134/ABCC1, Med. Sci. Monit. 24 (2018) 8831.
[49] T. Shuang, M. Wang, Y. Zhou, C. Shi, D. Wang, NF-κB1, c-Rel, and ELK1 inhibit miR-134 expression leading to TAB1 upregulation in paclitaxel-resistant human ovarian cancer, Oncotarget 8 (15) (2017) 24853.
[50] B. Xia, M. Lin, W. Dong, H. Chen, B. Li, X. Zhang, Y. Hou, G. Lou, Upregulation of miR-874-3p and miR-874-5p inhibits epithelial ovarian cancer malignancy via SIK2, J. Biochem. Mol. Toxicol. 32 (8) (2018), e22168.
[51] J. Yu, Y. Zhao, C. Liu, B. Hu, M. Zhao, Y. Ma, J. Jiang, Synergistic anti-tumor effect of paclitaxel and miR-34a combined with ultrasound microbubbles on cervical cancer in vivo and in vitro, Clin. Transl. Oncol. 22 (1) (2020) 60–69.
[52] Z. Fan, H. Cui, H. Yu, Q. Ji, L. Kang, B. Han, J. Wang, Q. Dong, Y. Li, Z. Yan, MiR-125a promotes paclitaxel sensitivity in cervical cancer through altering STAT3 expression, Oncogenesis 5 (2) (2016) e197.
[53] Z. Lu, Y. Xu, Y. Yao, S. Jiang, miR-205-5p contributes to paclitaxel resistance and progression of endometrial cancer by downregulating FOXO1, Oncol. Res. Featur. Preclin. Clin. Cancer Ther. (2020).
[54] B. Lang, C. Shang, Li-rong Meng, Targeted silencing of S100A8 gene by miR-24 to increase chemotherapy sensitivity of endometrial carcinoma cells to paclitaxel, Med. Sci. Monit. 22 (2016) 1953.
[55] W. Geng, H. Song, Q. Zhao, K. Dong, Q. Pu, H. Gao, Y. Lv, miR-520h stimulates drug resistance to paclitaxel by targeting the OTUD3-PTEN axis in breast cancer, Biomed Res. Int. 2020 (2020).
[56] Y. Wang, L. Yan, L. Zhang, H. Xu, T. Chen, Y. Li, H. Wang, S. Chen, W. Wang, C. Chen, NT21MP negatively regulates paclitaxel-resistant cells by targeting miR-155-3p and miR-155-5p via the CXCR4 pathway in breast cancer, Int. J. Oncol. 53 (3) (2018) 1043–1054.
[57] L. Tao, Y. Wu, S. Zhang, MiR-21-5p enhances the progression and paclitaxel resistance in drug-resistant breast cancer cell lines by targeting PDCD4, Neoplasma 2019 (2019).
[58] C. Ma, X. Shi, W. Guo, J. Niu, G. Wang, miR-107 enhances the sensitivity of breast cancer cells to paclitaxel, Open Med. (Wars) 14 (1) (2019) 456–466.
[59] H. Lyu, S. Wang, J. Huang, B. Wang, Z. He, B. Liu, Survivin-targeting miR-542-3p overcomes HER3 signaling-induced chemoresistance and enhances the antitumor activity of paclitaxel against HER2-overexpressing breast cancer, Cancer Lett. 420 (2018) 97–108.
[60] F. Asghari, N. Haghnavaz, D. Shanehbandi, V. Khaze, B. Baradaran, T. Kazemi, Differential altered expression of let-7a and miR-205 tumor-suppressor miRNAs in different subtypes of breast cancer under treatment with Taxol, Adv. Clin. Exp. Med. 27 (7) (2018) 941–945.
[61] H. Zang, Y. Li, X. Zhang, G. Huang, Circ-RNF111 contributes to paclitaxel resistance in breast cancer by elevating E2F3 expression via miR-140-5p, Thorac. Cancer (2020).
[62] J. Zhao, G.-Q. Jiang, MiR-4282 inhibits proliferation, invasion and metastasis of human breast cancer by targeting Myc, Eur. Rev. Med. Pharmacol. Sci. 22 (24) (2018) 8763–8771.
[63] Y.-k. Song, Y. Wang, Y.-y. Wen, P. Zhao, Zhi-Jie Bian, MicroRNA-22 suppresses breast cancer cell growth and increases paclitaxel sensitivity by targeting NRAS, Technol. Cancer Res. Treat. 17 (2018), 1533033818809997.
[64] M. Khordadmehr, R. Shahbazi, B. Baradaran, S. Sadreddini, D. Shanebandi, K. Hajiasgharzadeh, Restoring of miR-193a-5p sensitizes breast cancer cells to paclitaxel through P53 pathway, Adv. Pharm. Bull. 10 (4) (2020) 595–601.
[65] S. Irani, M. Paknejad, M. Soleimani, A. Soleimani, Evaluation of miR-34a effect on CCND1 mRNA level and sensitization of breast Cancer cell lines to paclitaxel, Iran. Biomed. J. 24 (6) (2020) 356–364.
[66] W. Wang, L. Zhang, Y. Wang, Y. Ding, T. Chen, Y. Wang, H. Wang, Y. Li, K. Duan, S. Chen, Q. Yang, C. Chen, Involvement of miR-451 in resistance to paclitaxel by regulating YWHAZ in breast cancer, Cell Death Dis. 8 (10) (2017) e3071.
[67] X. Fenfen, F. Yan, N. Zhenhua, L. Qiaoli, Z. Zhaowei, C. Zixi, H. Wenbin, Y. Honghong, W. Rong, X. Kang, Ursolic acid reverses the chemoresistance of breast cancer cells to paclitaxel by targeting mirna-149-5p/myd88, Front. Oncol. 9 (2019) 501.
[68] Y. Wang, H. Wang, Y. Ding, Y. Li, S. Chen, L. Zhang, H. Wu, J. Zhou, K. Duan, W. Wang, N-peptide of vMIP-II reverses paclitaxel-resistance by regulating miRNA-335 in breast cancer, Int. J. Oncol. 51 (3) (2017) 918–930.
[69] J.P. Gong, L. Yang, J.W. Tang, P. Sun, Q. Hu, J.W. Qin, X.M. Xu, B.C. Sun, Jin-Hai Tang, Overexpression of microRNA-24 increases the sensitivity to paclitaxel in drug-resistant breast carcinoma cell lines via targeting ABCB9, Oncol. Lett. 12 (5) (2016) 3905–3911.
[70] X. Tang, L. Jin, P. Cao, K. Cao, C. Huang, Y. Luo, J. Ma, S. Shen, M. Tan, X. Li, MicroRNA-16 sensitizes breast cancer cells to paclitaxel through suppression of IKBKB expression, Oncotarget 7 (17) (2016) 23668.
[71] X.-H. Liao, Y. Xiang, C.-X. Yu, J.-P. Li, H. Li, Q. Nie, P. Hu, J. Zhou, T.-C. Zhang, STAT3 is required for MiR-17-5p-mediated sensitization to chemotherapy-induced apoptosis in breast cancer cells, Oncotarget 8 (9) (2017) 15763.
[72] L. Zhang, T. Chen, L. Yan, H. Xu, Y. Wang, Y. Li, H. Wang, S. Chen, W. Wang, C. Chen, MiR-155-3p acts as a tumor suppressor and reverses paclitaxel resistance via negative regulation of MYD88 in human breast cancer, Gene 700 (2019) 85–95.
[73] X. Guan, Y. Guan, miR-145-5p attenuates paclitaxel resistance and suppresses the progression in drug-resistant breast cancer cell lines, Neoplasma 67 (5) (2020) 972–981.
[74] M. Wang, W.-R. Cai, R. Meng, J.-R. Chi, Y.-R. Li, A.-X. Chen, Y. Yu, X.-C. Cao, miR-485-5p suppresses breast cancer progression and chemosensitivity by targeting survivin, Biochem. Biophys. Res. Commun. 501 (1) (2018) 48–54.
[75] M.-m. Liu, Z. Li, X.-d. Han, J.-h. Shi, D.-y. Tu, W. Song, J. Zhang, X.-l. Qiu, Y. Ren, L.-l. Zhen, MiR-30e inhibits tumor growth and chemoresistance via targeting IRS1 in breast cancer, Sci. Rep. 7 (1) (2017) 1–10.
[76] Y.-Y. Wen, W.-T. Liu, H.-R. Sun, X. Ge, Z.-M. Shi, M. Wang, W. Li, J.-Y. Zhang, L.-Z. Liu, B.-H. Jiang, IGF-1-mediated PKM2/β-catenin/miR-152 regulatory circuit in breast cancer, Sci. Rep. 7 (1) (2017) 1–10.
[77] J. Chen, W. Tian, H. He, F. Chen, J. Huang, X. Wang, Z. Chen, Downregulation of miR-200c-3p contributes to the resistance of breast cancer cells to paclitaxel by targeting SOX2, Oncol. Rep. 40 (6) (2018) 3821–3829.

[78] Z. Zhou, C. Kennell, J.-Y. Lee, Y.-K. Leung, P. Tarapore, Calcium phosphate-polymer hybrid nanoparticles for enhanced triple negative breast cancer treatment via co-delivery of paclitaxel and miR-221/222 inhibitors, Nanomed. Nanotechnol. Biol. Med. 13 (2) (2017) 403–410.
[79] L. Sha, Y. Zhang, W. Wang, X. Sui, S. Liu, T. Wang, H. Zhang, MiR-18a upregulation decreases Dicer expression and confers paclitaxel resistance in triple negative breast cancer, Eur. Rev. Med. Pharmacol. Sci. 20 (11) (2016) 2201–2208.
[80] Y. Fan, Y. Dai, X. Wang, Y. Ren, J. Han, H. Zhang, MiR-18a upregulation enhances autophagy in triple negative cancer cells via inhibiting mTOR signaling pathway, Eur. Rev. Med. Pharmacol. Sci. 20 (11) (2016) 2194–2200.
[81] J. Hao, M. Lai, C. Liu, Expression of miR-335 in triple-negative breast cancer and its effect on chemosensitivity, J. BUON 24 (2019) 1526–1531.
[82] M. Liu, C. Gong, R. Xu, Y. Chen, X. Wang, MicroRNA-5195-3p enhances the chemosensitivity of triple-negative breast cancer to paclitaxel by downregulating EIF4A2, Cell. Mol. Biol. Lett. 24 (1) (2019) 47.
[83] H. Xiong, T. Yan, W. Zhang, F. Shi, X. Jiang, X. Wang, S. Li, Y. Chen, C. Chen, Y. Zhu, miR-613 inhibits cell migration and invasion by downregulating Daam1 in triple-negative breast cancer, Cell. Signal. 44 (2018) 33–42.
[84] Y. Wang, N. Wu, J. Zhang, H. Wang, X. Men, MiR-153-5p enhances the sensitivity of triple-negative breast cancer cells to paclitaxel by inducing G2M phase arrest, Onco. Ther. 13 (2020) 4089.
[85] H.-W. Chiu, H.-Y. Lin, J. Tseng, Y.-F. Lin, OTUD7B upregulation predicts a poor response to paclitaxel in patients with triple-negative breast cancer, Oncotarget 9 (1) (2018) 553.
[86] J. Liu, T. Meng, M. Yuan, L. Wen, B. Cheng, N. Liu, X. Huang, Y. Hong, H. Yuan, F. Hu, MicroRNA-200c delivered by solid lipid nanoparticles enhances the effect of paclitaxel on breast cancer stem cell, Int. J. Nanomed. 11 (2016) 6713.
[87] B. Zhang, R. Zhao, Y. He, X. Fu, L. Fu, Z. Zhu, L. Fu, J.-T. Dong, Micro RNA 100 sensitizes luminal A breast cancer cells to paclitaxel treatment in part by targeting mTOR, Oncotarget 7 (5) (2016) 5702.
[88] V. Stiegelbauer, P. Vychytilova-Faltejskova, M. Karbiener, A.-M. Pehserl, A. Reicher, M. Resel, E. Heitzer, C. Ivan, M. Bullock, H. Ling, miR-196b-5p regulates colorectal cancer cell migration and metastases through interaction with HOXB7 and GALNT5, Clin. Cancer Res. 23 (17) (2017) 5255–5266.
[89] M. Pichler, V. Stiegelbauer, P. Vychytilova-Faltejskova, C. Ivan, H. Ling, E. Winter, X. Zhang, M. Goblirsch, A. Wulf-Goldenberg, M. Ohtsuka, Genome-wide miRNA analysis identifies miR-188-3p as a novel prognostic marker and molecular factor involved in colorectal carcinogenesis, Clin. Cancer Res. 23 (5) (2017) 1323–1333.
[90] L. Yuan, L. Li, J. Liu, J. Mei, C.J. Lei, Down-regulation of miR-29a facilitates apoptosis of colorectal carcinoma cell SW480 and suppresses its Paclitaxel resistance, Eur. Rev. Med. Pharmacol. Sci. 22 (17) (2018) 5499–5507.
[91] H. Zhang, T. Deng, R. Liu, T. Ning, H. Yang, D. Liu, Q. Zhang, D. Lin, S. Ge, M. Bai, CAF secreted miR-522 suppresses ferroptosis and promotes acquired chemo-resistance in gastric cancer, Mol. Cancer 19 (1) (2020) 1–17.
[92] Y. Huang, G. Chen, Y. Wang, R. He, J. Du, X. Jiao, Q. Tai, Inhibition of microRNA-16 facilitates the paclitaxel resistance by targeting IKBKB via NF-κB signaling pathway in hepatocellular carcinoma, Biochem. Biophys. Res. Commun. 503 (2) (2018) 1035–1041.
[93] B.-y. Fei, X.-y. Wang, X.-d. Fang, MicroRNA-143 replenishment re-sensitizes colorectal cancer cells harboring mutant, but not wild-type, KRAS to paclitaxel treatment, Tumour Biol. 37 (5) (2016) 5829–5835.
[94] Y. Liu, S. Gao, X. Chen, M. Liu, C. Mao, X. Fang, Overexpression of miR-203 sensitizes paclitaxel (Taxol)-resistant colorectal cancer cells through targeting the salt-inducible kinase 2 (SIK2), Tumour Biol. 37 (9) (2016) 12231–12239.
[95] B. Zhao, J. Zhang, X. Chen, H. Xu, B. Huang, Mir-26b inhibits growth and resistance to paclitaxel chemotherapy by silencing the CDC6 gene in gastric cancer, Arch. Med. Sci. 15 (2) (2019) 498.
[96] L. Li, C. Wu, Y. Zhao, miRNA-34a enhances the sensitivity of gastric cancer cells to treatment with paclitaxel by targeting E2F5, Oncol. Lett. 13 (6) (2017) 4837–4842.
[97] H. Zheng, J.-J. Wang, X.-R. Yang, Y.-L. Yu, Upregulation of miR-34c after silencing E2F transcription factor 1 inhibits paclitaxel combined with cisplatin resistance in gastric cancer cells, World J. Gastroenterol. 26 (5) (2020) 499.
[98] B. Li, X. Jin, H. Meng, B. Hu, T. Zhang, J. Yu, S. Chen, X. Guo, W. Wang, W. Jiang, J. Wang, Morin promotes prostate cancer cells chemosensitivity to paclitaxel through miR-155/GATA3 axis, Oncotarget 8 (29) (2017) 47849.
[99] L. Chen, H. Cao, Y. Feng, MiR-199a suppresses prostate cancer paclitaxel resistance by targeting YES1, World J. Urol. 36 (3) (2018) 357–365.
[100] D. Wen, Y. Peng, F. Lin, R.K. Singh, R.I. Mahato, Micellar delivery of miR-34a modulator rubone and paclitaxel in resistant prostate cancer, Cancer Res. 77 (12) (2017) 3244–3254.
[101] X. Liu, X. Luo, Y. Wu, D. Xia, W. Chen, Z. Fang, J. Deng, Y. Hao, X. Yang, T. Zhang, MicroRNA-34a attenuates paclitaxel resistance in prostate cancer cells via direct suppression of JAG1/Notch1 axis, Biochemistry 50 (1) (2018) 261–276.
[102] Y. Li, L. Zhao, N. Li, Y. Miao, H. Zhou, L. Jia, miR-9 regulates the multidrug resistance of chronic myelogenous leukemia by targeting ABCB1, Oncol. Rep. 37 (4) (2017) 2193–2200.
[103] L. Huang, C. Hu, H. Chao, R. Wang, H. Lu, H. Li, H. Chen, miR-29c regulates resistance to paclitaxel in nasopharyngeal cancer by targeting ITGB1, Exp. Cell Res. 378 (1) (2019) 1–10.
[104] Y. Wang, L. Wang, miR-34a attenuates glioma cells progression and chemoresistance via targeting PD-L1, Biotechnol. Lett. 39 (10) (2017) 1485–1492.
[105] Y. Wang, L. Li, M. Qiu, B.-S. Gong, Effects of paclitaxel combined with miR-448 on growth and proliferation of bladder cancer EJ cells, Eur. Rev. Med. Pharmacol. Sci. 22 (11) (2018) 3363–3369.
[106] R. Begolli, N. Sideris, A. Giakountis, LncRNAs as chromatin regulators in cancer: from molecular function to clinical potential, Cancers 11 (10) (2019) 1524.
[107] J. Han, B. Han, X. Wu, J. Hao, X. Dong, Q. Shen, H. Pang, Knockdown of lncRNA H19 restores chemo-sensitivity in paclitaxel-resistant triple-negative breast cancer through triggering apoptosis and regulating Akt signaling pathway, Toxicol. Appl. Pharmacol. 359 (2018) 55–61.
[108] C. Cao, G. Sun, C. Liu, Long non-coding RNA SNHG6 regulates the sensitivity of prostate cancer cells to paclitaxel by sponging miR-186, Cancer Cell Int. 20 (1) (2020) 1–13.
[109] 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 (48) (2017) 84086.
[110] 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 (2) (2017) 243–250.
[111] 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 (10) (2019) 1061–1067.
[112] R. Xu, Y. Mao, K. Chen, W. He, W. Shi, Y. Han, The long noncoding RNA ANRIL acts as an oncogene and contributes to paclitaxel resistance of lung adenocarcinoma A549 cells, Oncotarget 8 (24) (2017) 39177.
[113] X. Tian, S. Gao, Y. Liu, Y. Xuan, R. Wu, Z. Zhang, Long non-coding RNA ENST00000500843 is downregulated and promotes chemoresistance to paclitaxel in lung adenocarcinoma, Oncol. Lett. 18 (4) (2019) 3716–3722.
[114] M. Ghaffarzadeh, H. Ghaedi, B. Alipoor, M.D. Omrani, F. Kazerouni, M. Shanaki, A. Labbaf, H. Pashaiefar, A. Rahimipour, Association of miR-149 (RS2292832) variant with the risk of coronary artery disease, J. Med. Biochem. 36 (3) (2017) 251–258.
[115] B.-D. Mao, P. Xu, Y. Zhong, W.-W. Ding, Q.-Z. Meng, LINC00511 knockdown prevents cervical cancer cell proliferation and reduces resistance to paclitaxel, J. Biosci. 44 (2) (2019) 44.
[116] C. Shi, M. Wang, LINC01118 modulates paclitaxel resistance of epithelial ovarian cancer by regulating miR-134/ABCC1, Med. Sci. Monitor: Int. Med. J. Exp. Clin. Res. 24 (2018) 8831.
[117] J. Wang, C. Ye, J. Liu, Y. Hu, UCA1 confers paclitaxel resistance to ovarian cancer through miR-129/ABCB1 axis, Biochem. Biophys. Res. Commun. 501 (4) (2018) 1034–1040.
[118] Z. Li, X. Wang, Y. Dang, X. Zhu, Y. Zhang, B. Cai, L. Zheng, Long non-coding RNA UCA1 promotes the progression of paclitaxel resistance in ovarian cancer by regulating the miR-654-5p/SIK2 axis, Eur. Rev. Med. Pharmacol. Sci. 24 (2020) 591–603.
[119] H. Zhao, A. Wang, Z. Zhang, LncRNA SDHAP1 confers paclitaxel resistance of ovarian cancer by regulating EIF4G2 expression via miR-4465, J. Biochem. (2020).
[120] L. Gu, Q. Li, H. Liu, X. Lu, M. Zhu, Long noncoding RNA TUG1 promotes autophagy-associated paclitaxel resistance by sponging miR-29b-3p in ovarian cancer cells, Onco. Ther. 13 (2020) 2007.
[121] J. Jiang, S. Wang, Z. Wang, J. Cai, L. Han, L. Xie, Q. Han, W. Wang, Y. Zhang, X. He, HOTAIR promotes paclitaxel resistance by regulating CHEK1 in ovarian cancer, Cancer Chemother. Pharmacol. 86 (2) (2020) 295–305.
[122] M. Zhang, S. Liu, C. Fu, X. Wang, M. Zhang, G. Liu, C. Dai, Z. Gong, H. Xu, Z. Fu, Lnc R.N.A. KB-1471A8. 2 overexpression suppresses cell proliferation and migration and antagonizes the paclitaxel resistance of ovarian cancer cells, Cancer Biother. Radiopharm. 34 (5) (2019) 316–324.
[123] S. Zou, X. Du, H. Lin, P. Wang, M. Li, Paclitaxel inhibits the progression of cervical cancer by inhibiting autophagy via lncRNARP11-381N20. 2, Eur. Rev. Med. Pharmacol. Sci. 22 (10) (2018) 3010–3017.
[124] C. Shang, C.N. Ao, C.C. Cheong, L. Meng, Long non-coding RNA CDKN2B antisense RNA 1 gene contributes to paclitaxel resistance in endometrial carcinoma, Front. Oncol. 9 (2019) 27.
[125] J.-L. Guo, T. Tang, J.-H. Li, Y.-H. Yang, L. Zhang, Y. Quan, LncRNA HEIH enhances paclitaxel-tolerance of endometrial cancer cells via activation of MAPK Signaling pathway, Pathol. Oncol. Res. 26 (3) (2020) 1757–1766.
[126] Q. Wang, W. Zhang, S. Hao, LncRNA CCAT1 modulates the sensitivity of paclitaxel in nasopharynx cancers cells via miR-181a/CPEB2 axis, Cell Cycle 16 (8) (2017) 795–801.
[127] S. Ren, G. Li, C. Liu, T. Cai, Z. Su, M. Wei, L. She, Y. Tian, Y. Qiu, X. Zhang, Next generation deep sequencing identified a novel lncRNA n375709 associated with paclitaxel resistance in nasopharyngeal carcinoma, Oncol. Rep. 36 (4) (2016) 1861–1867.
[128] H. Zhu, Silencing long non-coding RNA H19 combined with paclitaxel inhibits nasopharyngeal carcinoma progression, Int. J. Pediatr. Otorhinolaryngol. 138 (2020), 110249.
[129] H. Zhang, B. Zhao, X. Wang, F. Zhang, W. Yu, LINC00511 knockdown enhances paclitaxel cytotoxicity in breast cancer via regulating miR-29c/CDK6 axis, Life Sci. 228 (2019) 135–144.
[130] J. Chen, M. Zhu, L. Zou, J. Xia, J. Huang, Q. Deng, R. Xu, Long non-coding RNA LINC-PINT attenuates paclitaxel resistance in triple-negative breast cancer cells via targeting the RNA-binding protein NONO, Acta Biochim. Biophys. Sin. 52 (8) (2020) 801–809.
[131] R. Wang, T. Zhang, Z. Yang, C. Jiang, J. Seng, Long non-coding RNA FTH 1P3 activates paclitaxel resistance in breast cancer through miR-206/ABCB 1, J. Cell. Mol. Med. 22 (9) (2018) 4068–4075.

[132] Y. Pan, Y. Pan, Y. Cheng, F. Yang, Z. Yao, O. Wang, Knockdown of LncRNA MAPT-AS1 inhibites proliferation and migration and sensitizes cancer cells to paclitaxel by regulating MAPT expression in ER-negative breast cancers, Cell Biosci. 8 (1) (2018) 7.
[133] P. Zheng, L. Dong, B. Zhang, J. Dai, Y. Zhang, Y. Wang, S. Qin, Long noncoding RNA CASC2 promotes paclitaxel resistance in breast cancer through regulation of miR-18a-5p/CDK19, Histochem. Cell Biol. 152 (4) (2019) 281–291.
[134] C. Liu, F. Jiang, X. Zhang, X. Xu, Long non-coding RNA UCA1 modulates paclitaxel resistance in breast cancer via miR-613/CDK12 Axis, Cancer Manag. Res. 12 (2020) 2777.
[135] H. Wu, J. Gu, D. Zhou, W. Cheng, Y. Wang, Q. Wang, X. Wang, LINC00160 mediated paclitaxel-and doxorubicin-resistance in breast cancer cells by regulating TFF3 via transcription factor C/EBPβ, J. Cell. Mol. Med. 24 (15) (2020) 8589–8602.
[136] Y.Y. Wang, L. Yan, S. Yang, H.N. Xu, T.T. Chen, Z.Y. Dong, S.L. Chen, W.R. Wang, Q.L. Yang, C.J. Chen, Long noncoding RNA AC073284. 4 suppresses epithelial–mesenchymal transition by sponging miR-18b-5p in paclitaxel-resistant breast cancer cells, J. Cell. Physiol. 234 (12) (2019) 23202–23215.
[137] H. Wang, R. Qin, A. Guan, Y. Yao, Y. Huang, H. Jia, W. Huang, J. Gao, HOTAIR enhanced paclitaxel and doxorubicin resistance in gastric cancer cells partly through inhibiting miR-217 expression, J. Cell. Biochem. 119 (9) (2018) 7226–7234.
[138] Y. Duan, J. Chen, Y. Yang, Z. Qu, Y. Lu, D. Sun, LncRNA HOTAIR contributes Taxol-resistance of hepatocellular carcinoma cells via activating AKT phosphorylation by down-regulating miR-34a, Biosci. Rep. 40 (7) (2020).
[139] C. Liu, J. Hou, F. Shan, L. Wang, H. Lu, T. Ren, Long non-coding RNA CRNDE promotes colorectal carcinoma cell progression and paclitaxel resistance by regulating miR-126-5p/ATAD2 Axis, Onco. Ther. 13 (2020) 4931–4942.
[140] H. Zhao, Z. Zhang, B. Shi, X. Jiang, DANCR sponges miR-135a to regulate paclitaxel sensitivity in prostate cancer, Eur. Rev. Med. Pharmacol. Sci. 23 (16) (2019) 6849–6857.
[141] J. He, M. Sun, H. Geng, S. Tian, Long non-coding RNA Linc00518 promotes paclitaxel resistance of the human prostate cancer by sequestering miR-216b-5p, Biol. Cell 111 (2) (2019) 39–50.
[142] O. Bida, M. Gidoni, D. Ideses, S. Efroni, D. Ginsberg, A novel mitosis-associated lncRNA, MA-linc1, is required for cell cycle progression and sensitizes cancer cells to Paclitaxel, Oncotarget 6 (29) (2015) 27880.
[143] X. Ren, J. Cai, Y. Wang, X. Zhu, J. Qian, C. Han, X. Chen, LncRNA ADAMTS9-AS2 in osteosarcoma inhibits cell proliferation and enhances paclitaxel sensitivity by suppressing microRNA-130a-5p, Eur. J. Inflamm. 18 (2020), 2058739220934560.
[144] Z. Chen, Q. Zhuang, K. Cheng, Y. Ming, Y. Zhao, Q. Ye, S. Zhang, Long non-coding RNA TCL6 enhances preferential toxicity of paclitaxel to renal cell carcinoma cells, J. Cancer 11 (6) (2020) 1383.
[145] V. Němcová-Fürstová, D. Kopperová, K. Balušíková, M. Ehrlichová, V. Brynychová, R. Václavíková, P. Daniel, P. Souček, J. Kovář, Characterization of acquired paclitaxel resistance of breast cancer cells and involvement of ABC transporters, Toxicol. Appl. Pharmacol. 310 (2016) 215–228.
[146] H. Samli, M. Samli, B. Vatansever, S. Ardicli, N. Aztopal, D. Dincel, A. Sahin, F. Balci, Paclitaxel resistance and the role of miRNAs in prostate cancer cell lines, World J. Urol. 37 (6) (2019) 1117–1126.
[147] T. Liu, H. Sun, S. Liu, Z. Yang, L. Li, N. Yao, S. Cheng, X. Dong, X. Liang, C. Chen, The suppression of DUSP5 expression correlates with paclitaxel resistance and poor prognosis in basal-like breast cancer, Int. J. Med. Sci. 15 (7) (2018) 738.
[148] F. Asghari, N. Haghnavaz, D. Shanehbandi, V. Khaze, B. Baradaran, T. Kazemi, Differential altered expression of let-7a and miR-205 tumor-suppressor miRNAs in different subtypes of breast cancer under treatment with Taxol, Adv. Clin. Exp. Med. 27 (7) (2018) 941–945.
[149] M. Giai, N. Biglia, P. Sismondi, Chemoresistance in breast tumors, Eur. J. Gynaecol. Oncol. 12 (5) (1991) 359–373.
[150] A.V. Gudkov, C.R. Zelnick, A.R. Kazarov, R. Thimmapaya, D.P. Suttle, W.T. Beck, I.B. Roninson, Isolation of genetic suppressor elements, inducing resistance to topoisomerase II-interactive cytotoxic drugs, from human topoisomerase II cDNA, Proc. Natl. Acad. Sci. U. S. A. 90 (8) (1993) 3231–3235.
[151] C. Dumontet, B.I. Sikic, Mechanisms of action of and resistance to antitubulin agents: microtubule dynamics, drug transport, and cell death, J. Clin. Oncol. 17 (3) (1999) 1061.
[152] C. Marquette, L. Nabell, Chemotherapy-resistant metastatic breast cancer, Curr. Treat. Options Oncol. 13 (2) (2012) 263–275.
[153] T. Shuang, M. Wang, Y. Zhou, C. Shi, D. Wang, NF-κB1, c-Rel, and ELK1 inhibit miR-134 expression leading to TAB1 upregulation in paclitaxel-resistant human ovarian cancer, Oncotarget 8 (15) (2017) 24853.
[154] A. Saber, B. Liu, P. Ebrahimi, H.J. Haisma, CRISPR/Cas9 for overcoming drug resistance in solid tumors, DARU J. Pharm. Sci. (2019) 1–10.
[155] Z.-Y. He, Y.-G. Zhang, Y.-H. Yang, C.-C. Ma, P. Wang, W. Du, L. Li, R. Xiang, X.-R. Song, X. Zhao, In vivo ovarian cancer gene therapy using CRISPR-Cas9, Hum. Gene Ther. 29 (2) (2018) 223–233.
[156] X. Chen, X. Sun, J. Guan, J. Gai, J. Xing, L. Fu, F. Shen, K. Chen, W. Li, L. Han, Rsf-1 influences the sensitivity of non-small cell lung cancer to paclitaxel by regulating NF-κB pathway and its downstream proteins, Cell. Physiol. Biochem. 44 (6) (2017) 2322–2336.
[157] P.D. Hsu, E.S. Lander, F. Zhang, Development and applications of CRISPR-Cas9 for genome engineering, Cell 157 (6) (2014) 1262–1278.
[158] M. Jinek, K. Chylinski, I. Fonfara, M. Hauer, J.A. Doudna, E. Charpentier, A programmable dual-RNA–guided DNA endonuclease in adaptive bacterial immunity, Science 337 (6096) (2012) 816–821.
[159] Y. Chen, Y. Zhang, Application of the CRISPR/Cas9 system to drug resistance in breast cancer, Adv. Sci. 5 (6) (2018), 1700964.
[160] H. Lyu, S. Wang, J. Huang, B. Wang, Z. He, B. Liu, Survivin-targeting miR-542-3p overcomes HER3 signaling-induced chemoresistance and enhances the antitumor activity of paclitaxel against HER2-overexpressing breast cancer, Cancer Lett. 420 (2018) 97–108.
[161] J. Jiang, C. Xie, Y. Liu, Q. Shi, Y. Chen, Up-regulation of miR-383-5p suppresses proliferation and enhances chemosensitivity in ovarian cancer cells by targeting TRIM27, Biomed. Pharmacother. 109 (2019) 595–601.
[162] C.L.A. Yeung, N.-N. Co, T. Tsuruga, T.-L. Yeung, S.-Y. Kwan, C.S. Leung, Y. Li, E. S. Lu, K. Kwan, K.-K. Wong, Exosomal transfer of stroma-derived miR21 confers paclitaxel resistance in ovarian cancer cells through targeting APAF1, Nat. Commun. 7 (1) (2016) 1–14.
[163] G. Du, D. Cao, L. Meng, miR-21 inhibitor suppresses cell proliferation and colony formation through regulating the PTEN/AKT pathway and improves paclitaxel sensitivity in cervical cancer cells, Mol. Med. Rep. 15 (5) (2017) 2713–2719.
[164] J.A. Doudna, E. Charpentier, The new frontier of genome engineering with CRISPR-Cas9, Science 346 (6213) (2014).
[165] F.A. Ran, P.D. Hsu, J. Wright, V. Agarwala, D.A. Scott, F. Zhang, Genome engineering using the CRISPR-Cas9 system, Nat. Protoc. 8 (11) (2013) 2281–2308.
[166] J.-P. Zhang, X.-L. Li, G.-H. Li, W. Chen, C. Arakaki, G.D. Botimer, D. Baylink, L. Zhang, W. Wen, Y.-W. Fu, Efficient precise knockin with a double cut HDR donor after CRISPR/Cas9-mediated double-stranded DNA cleavage, Genome Biol. 18 (1) (2017) 1–18.
[167] J. Mianné, L. Chessum, S. Kumar, C. Aguilar, G. Codner, M. Hutchison, A. Parker, A.-M. Mallon, S. Wells, M.M. Simon, Correction of the auditory phenotype in C57BL/6N mice via CRISPR/Cas9-mediated homology directed repair, Genome Med. 8 (1) (2016) 16.
[168] P. Gangadaran, B.-C. Ahn, Extracellular vesicle-and extracellular. Vesicle mimetics-based drug delivery systems: new perspectives, challenges, and clinical developments, Pharmaceutics 12 (5) (2020) 442.
[169] S.-H. Chiou, I.P. Winters, J. Wang, S. Naranjo, C. Dudgeon, F.B. Tamburini, J. J. Brady, D. Yang, B.M. Grüner, C.-H. Chuang, Pancreatic cancer modeling using retrograde viral vector delivery and in vivo CRISPR/Cas9-mediated somatic genome editing, Genes Dev. 29 (14) (2015) 1576–1585.
[170] F. Schmidt, D. Grimm, CRISPR genome engineering and viral gene delivery: a case of mutual attraction, Biotechnol. J. 10 (2) (2015) 258–272.
[171] C. Liang, F. Li, L. Wang, Z.-K. Zhang, C. Wang, B. He, J. Li, Z. Chen, A.B. Shaikh, J. Liu, Tumor cell-targeted delivery of CRISPR/Cas9 by aptamer-functionalized lipopolymer for therapeutic genome editing of VEGFA in osteosarcoma, Biomaterials 147 (2017) 68–85.
[172] D. Yu-Wei, Z.s. Li, S.m. Xiong, G. Huang, Y.f. Luo, T.y. Huo, M.h. Zhou, Y. w. Zheng, Paclitaxel induces apoptosis through the TAK1–JNK activation pathway, FEBS Open Bio 10 (8) (2020) 1655–1667.
[173] A.S. Azmi, H.Y. Khan, I. Muqbil, A. Aboukameel, J.E. Neggers, D. Daelemans, A. Mahipal, G. Dyson, M. Kamgar, M.N. Al-Hallak, Preclinical assessment with clinical validation of selinexor with gemcitabine and nab-paclitaxel for the treatment of pancreatic ductal adenocarcinoma, Clin. Cancer Res. 26 (6) (2020) 1338–1348.
[174] B.W. Wardhani, M.U. Puteri, Y. Watanabe, M. Louisa, R. Setiabudy, M. Kato, TGF-β-induced TMEPAI attenuates the response of triple-negative breast cancer cells to doxorubicin and paclitaxel, J. Exp. Pharmacol. 12 (2020) 17.
[175] P. Sen, S. Ghosal, R. Hazra, R. Mohanty, S. Arega, B. Sahu, N. Ganguly, CRISPR-mediated knockdown of miR-214 modulates cell fate in response to anti-cancer drugs in HPV-negative and HPV-positive cervical cancer cells, J. Biosci. 45 (2020).
[176] W. Wei, Y. He, Y.-M. Wu, Identification of genes associated with SiHa cell sensitivity to paclitaxel by CRISPR-Cas9 knockout screening, Int. J. Clin. Exp. Pathol. 11 (4) (2018) 1972.
[177] G. Zhao, Q. Wang, Q. Gu, W. Qiang, J.-J. Wei, P. Dong, H. Watari, W. Li, J. Yue, Lentiviral CRISPR/Cas9 nickase vector mediated BIRC5 editing inhibits epithelial to mesenchymal transition in ovarian cancer cells, Oncotarget 8 (55) (2017) 94666.
[178] J. Ribeiro, C. Schorl, N. Yano, N. Romano, K. Kim, R. Singh, R. Moore, HE4 promotes collateral resistance to cisplatin and paclitaxel in ovarian cancer cells, J. Ovarian Res. 9 (1) (2016) 28.
[179] E.H. Stover, M.B. Baco, O. Cohen, Y.Y. Li, E.L. Christie, M. Bagul, A. Goodale, Y. Lee, S. Pantel, M.G. Rees, Pooled genomic screens identify anti-apoptotic genes as targetable mediators of chemotherapy resistance in ovarian cancer, Mol. Cancer Res. 17 (11) (2019) 2281–2293.
[180] M. Kodama, T. Kodama, J.Y. Newberg, H. Katayama, M. Kobayashi, S.M. Hanash, K. Yoshihara, Z. Wei, J.C. Tien, R. Rangel, In vivo loss-of-function screens identify KPNB1 as a new druggable oncogene in epithelial ovarian cancer, Proc. Natl. Acad. Sci. U. S. A. 114 (35) (2017) E7301–E7310.
[181] Y. Liao, L. Chen, Y. Feng, J. Shen, Y. Gao, G. Cote, E. Choy, D. Harmon, H. Mankin, F. Hornicek, Targeting programmed cell death ligand 1 by CRISPR/Cas9 in osteosarcoma cells, Oncotarget 8 (18) (2017) 30276.
[182] J. Yu, J. Zhou, F. Xu, W. Bai, W. Zhang, High expression of Aurora-B is correlated with poor prognosis and drug resistance in non-small cell lung cancer, Int. J. Biol. Markers 33 (2) (2018) 215–221.
[183] X.-Y. Wu, J. Fang, Z.-J. Wang, C. Chen, J.-Y. Liu, G.-N. Wu, X.-Q. Yao, F.-K. Liu, X. Zhou, Identification of RING-box 2 as a potential target for combating colorectal cancer growth and metastasis, Am. J. Cancer Res. 7 (6) (2017) 1238.
[184] Y. Cui, Q. Li, H. Li, Y. Wang, H. Wang, W. Chen, S. Zhang, J. Cao, T. Liu, Asparaginyl endopeptidase improves the resistance of microtubule-targeting drugs in gastric cancer through IQGAP1 modulating the EGFR/JNK/ERK signaling pathway, Onco. Ther. 10 (2017) 627.
[185] P. Zhao, H. Guan, Z. Dai, Y. Ma, Y. Zhao, D. Liu, Long noncoding RNA DLX6-AS1 promotes breast cancer progression via miR-505-3p/RUNX2 axis, Eur. J. Pharmacol. 865 (2019), 172778.

[186] X. Cao, L. Dang, X. Zheng, Y. Lu, Y. Lu, R. Ji, T. Zhang, X. Ruan, J. Zhi, X. Hou, Targeting super-enhancer-driven oncogenic transcription by CDK7 inhibition in anaplastic thyroid carcinoma, Thyroid 29 (6) (2019) 809–823.
[187] S. Huang, R. Tang, Y.P. Randy, BCL-W is a regulator of microtubule inhibitor-induced mitotic cell death, Oncotarget 7 (25) (2016) 38718.
[188] S.Y. Eom, S.-H. Hwang, H. Yeom, M. Lee, An ATG5 knockout promotes paclitaxel resistance in v-Ha-ras-transformed NIH 3T3 cells, Biochem. Biophys. Res. Commun. 513 (1) (2019) 234–241.
[189] S.-H. Hwang, H. Yeom, M. Lee, ATG5 knockout promotes paclitaxel sensitivity in drug-resistant cells via induction of necrotic cell death, Korean J. Physiol. Pharmacol. 24 (3) (2020) 233.
[190] K. Tu, H. Deng, L. Kong, Y. Wang, T. Yang, Q. Hu, M. Hu, C. Yang, Z. Zhang, Reshaping tumor immune microenvironment through acidity-responsive nanoparticles featured with CRISPR/Cas9-mediated programmed death-ligand 1 attenuation and chemotherapeutics-induced immunogenic cell death, ACS Appl. Mater. Interfaces 12 (14) (2020) 16018–16030.
[191] S. Ramanathan, G. Archunan, M. Sivakumar, S.T. Selvan, A.L. Fred, S. Kumar, B. Gulyás, P. Padmanabhan, Theranostic applications of nanoparticles in neurodegenerative disorders, Int. J. Nanomed. 13 (2018) 5561.
[192] H. Daraee, A. Eatemadi, E. Abbasi, S. Fekri Aval, M. Kouhi, A. Akbarzadeh, Application of gold nanoparticles in biomedical and drug delivery, Artif. Cells Nanomed. Biotechnol. 44 (1) (2016) 410–422.
[193] S. Gelperina, K. Kisich, M.D. Iseman, L. Heifets, The potential advantages of nanoparticle drug delivery systems in chemotherapy of tuberculosis, Am. J. Respir. Crit. Care Med. 172 (12) (2005) 1487–1490.
[194] G. Storm, S.O. Belliot, T. Daemen, D.D. Lasic, Surface modification of nanoparticles to oppose uptake by the mononuclear phagocyte system, Adv. Drug Deliv. Rev. 17 (1) (1995) 31–48.
[195] P. Ma, R.J. Mumper, Paclitaxel nano-delivery systems: a comprehensive review, J. Nanomed. Nanotechnol. 4 (2) (2013), 1000164.
[196] P. Schmid, S. Adams, H.S. Rugo, A. Schneeweiss, C.H. Barrios, H. Iwata, V. Diéras, R. Hegg, S.-A. Im, G. Shaw Wright, Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer, N. Engl. J. Med. 379 (22) (2018) 2108–2121.
[197] F. Ren, R. Chen, Y. Wang, Y. Sun, Y. Jiang, G. Li, Paclitaxel-loaded poly (n-butylcyanoacrylate) nanoparticle delivery system to overcome multidrug resistance in ovarian cancer, Pharm. Res. 28 (4) (2011) 897–906.
[198] L. Zou, Y.H. Di Wang, C. Fu, W. Li, L. Dai, L. Yang, J. Zhang, Drug resistance reversal in ovarian cancer cells of paclitaxel and borneol combination therapy mediated by PEG-PAMAM nanoparticles, Oncotarget 8 (36) (2017) 60453.
[199] N. Larson, J. Yang, A. Ray, D.L. Cheney, H. Ghandehari, J. Kopeček, Biodegradable multiblock poly (N-2-hydroxypropyl) methacrylamide gemcitabine and paclitaxel conjugates for ovarian cancer cell combination treatment, Int. J. Pharm. 454 (1) (2013) 435–443.
[200] S. Yin, C. Xia, Y. Wang, D. Wan, J. Rao, X. Tang, J. Wei, X. Wang, M. Li, Z. Zhang, Dual receptor recognizing liposomes containing paclitaxel and hydroxychloroquine for primary and metastatic melanoma treatment via autophagy-dependent and independent pathways, J. Control. Release 288 (2018) 148–160.
[201] Y. Zhong, T. Su, Q. Shi, Y. Feng, Z. Tao, Q. Huang, L. Li, L. Hu, S. Li, H. Tan, Co-administration of iRGD enhances tumor-targeted delivery and anti-tumor effects of paclitaxel-loaded PLGA nanoparticles for colorectal cancer treatment, Int. J. Nanomedicine 14 (2019) 8543.
[202] Z. Zhang, X. Wang, B. Li, Y. Hou, J. Yang, L. Yi, Development of a novel morphological paclitaxel-loaded PLGA microspheres for effective cancer therapy: in vitro and in vivo evaluations, Drug Deliv. 25 (1) (2018) 166–177.
[203] L.P. Ganipineni, B. Ucakar, N. Joudiou, J. Bianco, P. Danhier, M. Zhao, C. Bastiancich, B. Gallez, F. Danhier, V. Préat, Magnetic targeting of paclitaxel-loaded poly (lactic-co-glycolic acid)-based nanoparticles for the treatment of glioblastoma, Int. J. Nanomed. 13 (2018) 4509.
[204] C. Zhang, T. An, D. Wang, G. Wan, M. Zhang, H. Wang, S. Zhang, R. Li, X. Yang, Y. Wang, Stepwise pH-responsive nanoparticles containing charge-reversible pullulan-based shells and poly (β-amino ester)/poly (lactic-co-glycolic acid) cores as carriers of anticancer drugs for combination therapy on hepatocellular carcinoma, J. Control. Release 226 (2016) 193–204.
[205] Z. He, J. Huang, Y. Xu, X. Zhang, Y. Teng, C. Huang, Y. Wu, X. Zhang, H. Zhang, W. Sun, Co-delivery of cisplatin and paclitaxel by folic acid conjugated amphiphilic PEG-PLGA copolymer nanoparticles for the treatment of non-small lung cancer, Oncotarget 6 (39) (2015) 42150.
[206] X. Tang, S. Cai, R. Zhang, P. Liu, H. Chen, Y. Zheng, L. Sun, Paclitaxel-loaded nanoparticles of star-shaped cholic acid-core PLA-TPGS copolymer for breast cancer treatment, Nanoscale Res. Lett. 8 (1) (2013) 420.
[207] Q. Wang, C. Li, T. Ren, S. Chen, X. Ye, H. Guo, H. He, Y. Zhang, T. Yin, X.-J. Liang, Poly (vinyl methyl ether/maleic anhydride)-doped PEG–PLA nanoparticles for oral paclitaxel delivery to improve bioadhesive efficiency, Mol. Pharm. 14 (10) (2017) 3598–3608.
[208] F. Cui, Y. Li, S. Zhou, M. Jia, X. Yang, F. Yu, S. Ye, Z. Hou, L. Xie, A comparative in vitro evaluation of self-assembled PTX-PLA and PTX-MPEG-PLA nanoparticles, Nanoscale Res. Lett. 8 (1) (2013) 301.
[209] X. He, L. Li, H. Su, D. Zhou, H. Song, L. Wang, X. Jiang, Poly (ethylene glycol)-block-poly (ε-caprolactone)–and phospholipid-based stealth nanoparticles with enhanced therapeutic efficacy on murine breast cancer by improved intracellular drug delivery, Int. J. Nanomed. 10 (2015) 1791.
[210] E. Bernabeu, G. Helguera, M.J. Legaspi, L. Gonzalez, C. Hocht, C. Taira, D. A. Chiappetta, Paclitaxel-loaded PCL–TPGS nanoparticles: in vitro and in vivo performance compared with Abraxane®, Colloids Surf. B: Biointerfaces 113 (2014) 43–50.
[211] T. Zhao, H. Chen, Y. Dong, J. Zhang, H. Huang, J. Zhu, W. Zhang, Paclitaxel-loaded poly (glycolide-co-ε-caprolactone)-bD-α-tocopheryl polyethylene glycol 2000 succinate nanoparticles for lung cancer therapy, Int. J. Nanomed. 8 (2013) 1947.
[212] M. He, Z. Zhao, L. Yin, C. Tang, C. Yin, Hyaluronic acid coated poly (butyl cyanoacrylate) nanoparticles as anticancer drug carriers, Int. J. Pharm. 373 (1–2) (2009) 165–173.
[213] C.-Y. Huang, C.-M. Chen, Y.-D. Lee, Synthesis of high loading and encapsulation efficient paclitaxel-loaded poly (n-butyl cyanoacrylate) nanoparticles via miniemulsion, Int. J. Pharm. 338 (1–2) (2007) 267–275.
[214] C. Mugabe, B.A. Hadaschik, R.K. Kainthan, D.E. Brooks, A.I. So, M.E. Gleave, H. M. Burt, Paclitaxel incorporated in hydrophobically derivatized hyperbranched polyglycerols for intravesical bladder cancer therapy, BJU Int. 103 (7) (2009) 978–986.
[215] X. Zhang, X. Zhang, Z. Wu, X. Gao, C. Cheng, Z. Wang, C. Li, A hydrotropic β-cyclodextrin grafted hyperbranched polyglycerol co-polymer for hydrophobic drug delivery, Acta Biomater. 7 (2) (2011) 585–592.
[216] X. Zhang, X. Zhang, P. Yu, Y. Han, Y. Li, C. Li, Hydrotropic polymeric mixed micelles based on functional hyperbranched polyglycerol copolymers as hepatoma-targeting drug delivery system, J. Pharm. Sci. 102 (1) (2013) 145–153.
[217] C. Sarisozen, I. Vural, T. Levchenko, A.A. Hincal, V.P. Torchilin, Long-circulating PEG-PE micelles co-loaded with paclitaxel and elacridar (GG918) overcome multidrug resistance, Drug Deliv. 19 (8) (2012) 363–370.
[218] A.H. Abouzeid, N.R. Patel, V.P. Torchilin, Polyethylene glycol-phosphatidylethanolamine (PEG-PE)/vitamin E micelles for co-delivery of paclitaxel and curcumin to overcome multi-drug resistance in ovarian cancer, Int. J. Pharm. 464 (1–2) (2014) 178–184.
[219] C. Sarisozen, I. Vural, T. Levchenko, A.A. Hincal, V.P. Torchilin, PEG-PE-based micelles co-loaded with paclitaxel and cyclosporine A or loaded with paclitaxel and targeted by anticancer antibody overcome drug resistance in cancer cells, Drug Deliv. 19 (4) (2012) 169–176.
[220] D. Zhao, X. Zhao, Y. Zu, J. Li, Y. Zhang, R. Jiang, Z. Zhang, Preparation, characterization, and in vitro targeted delivery of folate-decorated paclitaxel-loaded bovine serum albumin nanoparticles, Int. J. Nanomedicine 5 (2010) 669.
[221] J. Gong, M. Huo, J. Zhou, Y. Zhang, X. Peng, D. Yu, H. Zhang, J. Li, Synthesis, characterization, drug-loading capacity and safety of novel octyl modified serum albumin micelles, Int. J. Pharm. 376 (1–2) (2009) 161–168.
[222] A. Almeida, D. Silva, V. Gonçalves, B. Sarmento, Synthesis and characterization of chitosan-grafted-polycaprolactone micelles for modulate intestinal paclitaxel delivery, Drug Deliv. Transl. Res. 8 (2) (2018) 387–397.
[223] W. Trickler, A. Nagvekar, A.K. Dash, A novel nanoparticle formulation for sustained paclitaxel delivery, AAPS PharmSciTech 9 (2) (2008) 486.
[224] M.-K. Jang, Y.-I. Jeong, J.-W. Nah, Characterization and preparation of core–shell type nanoparticle for encapsulation of anticancer drug, Colloids Surf. B: Biointerfaces 81 (2) (2010) 530–536.
[225] J.A. Zhang, G. Anyarambhatla, L. Ma, S. Ugwu, T. Xuan, T. Sardone, I. Ahmad, Development and characterization of a novel Cremophor® EL free liposome-based paclitaxel (LEP-ETU) formulation, Eur. J. Pharm. Biopharm. 59 (1) (2005) 177–187.
[226] Y. Pu, H. Zhang, Y. Peng, Q. Fu, Q. Yue, Y. Zhao, L. Guo, Y. Wu, Dual-targeting liposomes with active recognition of GLUT5 and αvβ3 for triple-negative breast cancer, Eur. J. Med. Chem. 183 (2019), 111720.
[227] M.C. Roque, M.S. Franco, J.M.C. Vilela, M.S. Andrade, A.L.B. de Barros, E. A. Leite, M.C. Oliveira, Development of long-circulating and fusogenic liposomes Co-encapsulating paclitaxel and doxorubicin in synergistic ratio for the treatment of breast cancer, Curr. Drug Deliv. 16 (9) (2019) 829–838.
[228] D.-B. Chen, T.-z. Yang, W.-L. Lu, Q. Zhang, In vitro and in vivo study of two types of long-circulating solid lipid nanoparticles containing paclitaxel, Chem. Pharm. Bull. 49 (11) (2001) 1444–1447.
[229] W. Xu, E.J. Bae, M.-K. Lee, Enhanced anticancer activity and intracellular uptake of paclitaxel-containing solid lipid nanoparticles in multidrug-resistant breast cancer cells, Int. J. Nanomed. 13 (2018) 7549.
[230] B. Gupta, B.K. Poudel, S. Regmi, S. Pathak, H.B. Ruttala, M. Gautam, G.J. An, J.-H. Jeong, H.-G. Choi, C.S. Yong, Paclitaxel and erlotinib-co-loaded solid lipid core nanocapsules: assessment of physicochemical characteristics and cytotoxicity in non-small cell lung cancer, Pharm. Res. 35 (5) (2018) 96.
[231] G. Lollo, M. Vincent, G. Ullio-Gamboa, L. Lemaire, F. Franconi, D. Couez, J.-P. Benoit, Development of multifunctional lipid nanocapsules for the co-delivery of paclitaxel and CpG-ODN in the treatment of glioblastoma, Int. J. Pharm. 495 (2) (2015) 972–980.
[232] J. Hureaux, F. Lagarce, F. Gagnadoux, L. Vecellio, A. Clavreul, E. Roger, M. Kempf, J.-L. Racineux, P. Diot, J.-P. Benoit, Lipid nanocapsules: ready-to-use nanovectors for the aerosol delivery of paclitaxel, Eur. J. Pharm. Biopharm. 73 (2) (2009) 239–246.
[233] S. Ganta, M. Amiji, Coadministration of paclitaxel and curcumin in nanoemulsion formulations to overcome multidrug resistance in tumor cells, Mol. Pharm. 6 (3) (2009) 928–939.
[234] P. Kan, Z.-B. Chen, C.-J. Lee, I.-M. Chu, Development of nonionic surfactant/phospholipid o/w emulsion as a paclitaxel delivery system, J. Control. Release 58 (3) (1999) 271–278.
[235] Y. Sugiyama, R. Yoshimi, M. Takeno, Y. Kunishita, D. Kishimoto, R. Kamiyama, Y. Kirino, S. Ohno, H. Nakajima, miR-1 is a novel biomarker for polymyositis/dermatomyositis-associated interstitial lung disease, Mod. Rheumatol. (2019) 1–6.