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REVIEW ARTICLE

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Noncoding RNAs and their therapeutics in paclitaxel chemotherapy: Mechanisms of initiation, progression, and drug sensitivity

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Abstract

The identification of agents that can reverse drug resistance in cancer chemotherapy, and enhance the overall efficacy is of great interest. Paclitaxel (PTX) belongs to taxane family

Abbreviations: 3′-UTR, 3′-untranslated region; ABC, ATP-binding cassette; Ago2, argonaute 2; Ai, antisense intronic; Akt, protein kinase B; APAF1, apoptotic protease activating factor 1; CAF, cancer-associated fibroblast; CDK6, cyclin-dependent kinase 6; CDK8, cyclin-dependent kinase 8; circRNA, circular RNA; DUSP7, dual specificity phosphatase 7; EMT, epithelial-to-mesenchymal transition; FOXO1, Forkhed box protein O1; FOXR2, Forkhead box 2; GATA3, GATA binding protein 3; HIF-1α, hypoxia inducible factor-1α; hnRNPA1, heterogenous nuclear ribonucleoprotein A1; ITGB1, integrin beta-1; lncRNA, long noncoding RNA; MAPK, mitogen-activated protein kinase; MDR1, multidrug resistance 1; miRNA, microRNA; mRNA, messenger RNA; MRP1, multidrug resistance-associated protein 1; ncRNA, noncoding RNA; PcG, polycomb group protein; PDCD4, programmed cell death 4; piRNA, PIWI-interacting RNA; pre-mRNA, precursor-mRNA; PTEN, phosphatase and tensin homolog; PTX, paclitaxel; P-gp, P-glycoprotein; RBP, RNA-binding protein; RGD, tripeptide arginine-glycine-aspartic sequence; RISC, RNA-Induced Silencing Group; RNAi, RNA interference; shRNA, short-hairpin RNA; SIK2, serine/threonine-protein kinase 2; siRNA, small interfering RNA; SLN, solid lipid nanoparticle; Sp1, specificity protein 1; STAT3, signal transducer and activator of transcription 3; TAB3, TAK1-binding protein 3; TAK1, transforming growth factor β-activated protein kinase 1; TP53INP1, tumor protein p53-indicoble nuclear protein 1; TRIM27, tripartite motif-containing protein 27; TRIM65, tripartite motif-containing protein 65; UPS7, ubiquitin-specific protease 7; YES1, Yamaguchi sarcoma viral homolog 1; ZEB1, zinc finger E-box binding homeobox 1.

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that exerts an antitumor effect by stabilizing microtubules and inhibiting cell cycle progression. However, PTX resistance often develops in tumors due to the overexpression of drug transporters and tumor-promoting pathways. Noncoding RNAs (ncRNAs) are modulators of many processes in cancer cells, such as apoptosis, migration, differentiation, and angiogenesis. In the present study, we summarize the effects of ncRNAs on PTX chemotherapy. MicroRNAs (miRNAs) can have opposite effects on PTX resistance (stimulation or inhibition) via influencing YES1, SK2, MRP1, and STAT3. Moreover, miRNAs modulate the growth and migration rates of tumor cells in regulating PTX efficacy. PIWI-interacting RNAs, small interfering RNAs, and short-hairpin RNAs are other members of ncRNAs regulating PTX sensitivity of cancer cells. Long noncoding RNAs (LncRNAs) are similar to miRNAs and can modulate PTX resistance/sensitivity by their influence on miRNAs and drug efflux transport. The cytotoxicity of PTX against tumor cells can also be affected by circular RNAs (circRNAs) and limitation is that oncogenic circRNAs have been emphasized and experiments should also focus on onco-suppressor circRNAs.

KEYWORDS
circular RNA, long noncoding RNA, miRNA, paclitaxel, short-hairpin RNA, small interfering RNA

1 | INTRODUCTION

Chemotherapy drugs are the most often employed type of cancer treatments due to their ability to suppress cancer progression (Abadi, Mirzaei, et al., 2021; Ashrafizadeh, Mirzaei, et al., 2021; Delfi, Sartorius, et al., 2021), but drug resistance has led to chemotherapy failure and cancer patient deaths (Ashrafizade, Delfi, et al., 2021; Kirtonia, Ashrafizadeh, et al., 2021; Makvandi, Josic, et al., 2021; Mirzaei, Gholami, et al., 2021; Mirzaei, Gholami, et al., 2021; Sharifi, Bigham, et al., 2021). Paclitaxel (PTX) is a member of the taxane family that has demonstrated high antitumor activity against different tumor types, such as breast, lung, prostate, brain, and ovarian cancers (Ashrafizadeh, Ahmadi, et al., 2020; Ashrafizadeh, Zarrabi, et al., 2020; Kirtonia, Ashrafizadeh, et al., 2021). Similar to other taxanes, PTX prevents cancer cell proliferation and progression via the cell cycle by stabilizing microtubules and inhibiting tubulin depolymerization. In fact, the balance of microtubules is disrupted by PTX (Bernabeu, Cagel, et al., 2017; Hwang, Kim, et al., 2019; Lee, Kim, et al., 2018; Nyrop, Deal, et al., 2019; Rajendran, Li, et al., 2011). Despite showing promising results in many clinical studies (Vergote, Bergfeldt, et al., 2020), cancer cells can develop resistance to PTX chemotherapy. Although many of the factors involved in PTX resistance are understood, there are additional causes that have not been completely elucidated. Different strategies have been applied to overcome PTX resistance, for instance by loading PTX onto nanoparticles to promote its targeted delivery and accumulation in tumors. Nanostructures can significantly enhance the efficacy of PTX chemotherapy and are associated with apoptosis induction in cancer cells (Diab, Alkafaas, et al., 2020; Fraguas-Sánchez, Fernández-Carballido, et al., 2020; Tang, Chen, et al., 2020). Another strategy is to combine PTX with drugs to suppress PTX resistance and overcome drug efflux from cancer cells (Attia, El-Kersh, et al., 2020; Khan, Quispe, et al., 2020; Saghatelyan, Tananyan, et al., 2020; Zhang, Huang, et al., 2020). A third strategy is signaling network recognition participating in PTX resistance, which may be overcome by pharmacological and genetic interventions (Vergote, Bergfeldt, et al., 2020; Wang, Min, et al., 2020). ncRNAs, including miRNAs, lncRNAs, and circRNAs, are all potential regulators of the cancer cell response to chemotherapy (Ashrafizaveh, Ashrafizadeh, et al., 2021; Delfi, Sartorius, et al., 2021; Guan, Zhang, et al., 2020; Kirtonia, Ashrafizadeh, et al., 2021; Mirzaei et al., 2021; Paskeh, Mirzaei, et al., 2021; Shen, Lei, et al., 2020; Wang, Ji, et al., 2020; Zhang, Huang, et al., 2020; Zhou, Jiang, et al., 2020; Zhou, Wei, et al., 2020). Although there are some ncRNAs that can mediate chemoresistance, others have the opposite effect and can suppress chemoresistance by sensitizing cancer cells to chemotherapy-mediated apoptosis and cell cycle arrest (Chen, Zhu, et al., 2020; Zheng, Li, et al., 2020; Zou, Yang, et al., 2020). The current study focuses on the role of ncRNAs and exosomal ncRNAs in regulating PTX response of tumor cells.

2 | NONCODING RNAs

2.1 | Short noncoding RNAs

2.1.1 | MicroRNAs

miRNAs were first discovered in 1993, when Ambros et al. found that *lin-4* gene, known as lin-4 miRNA can diminish lin-4 protein levels via antisense complementary binding of RNA transcripts (Bautista-Sánchez, Arriaga-Canon, et al., 2020; Lee, Feinbaum, et al., 1993). This research was related to *Caemorhabditis elegans* and further

experiment detected other miRNA genes in various species, including human. Consequently, miRNAs were established as small regulatory RNAs with length of 19–24 nucleotides with presence in both intergenic and intragenic sections of genome (Ambros, Bartel, et al., 2003; Mirzaei, Saebfar, et al., 2021; Mirzaei, Zarrabi, et al., 2021). These endogenous noncoding RNAs are capable of gene downregulation (Indrieri, Carrella, et al., 2020). The inhibitory impact of miRNAs on gene expression is mediated by imperfect binding to sequences located at 3′-untranslated region (3′-UTR; Bartel, 2004). It is worth mentioning that miRNAs can also promote gene expression level (Ashrafizadeh et al., 2020; O'Brien, Hayder, et al., 2018). The identification of target sequence that miRNAs bind to is directed by "seed region" containing 7–8 nucleotides that have been located at positions 2–7 from miRNA 5′region (Filipowicz, Jaskiewicz, et al., 2005; Jing, Huang, et al., 2005). Based on the recognition of binding site, the binding of miRNA-induced silencing complex to cognate target results in various outcomes (Pillai, Bhattacharyya, et al., 2007). The suppression of translation occurs when binding is partial complementary, while degradation of target transcript occurs in fully complementary binding (Bartel, 2004; Filipowicz, Jaskiewicz, et al., 2005; Krol, Loedige, et al., 2010). It is also worth mentioning that small RNAs have the capacity of modifying chromatin and they can affect gene expression by targeting RNA interference pathways (Holoch & Moazed, 2015).

The fact that a variety of genes and pathways are regulated by miRNAs and more importantly, deregulation of miRNAs occurs in diseases, particularly cancer, has made them appropriate options to consider in disease and cancer therapy (Ashrafizadeh, Zarrabi, et al., 2020; Ashrafizadeh, Zarrabi, et al., 2020; Ashrafizadeh, Zarrabi, et al., 2020; Vinchure & Kulshreshtha, 2020). Overall, it appears that miRNAs that undergo upregulation in disease, lead to disease progression, while downregulated miRNAs exert a protective role. The miRNA inhibition and replacement therapeutic strategies have been developed for targeting these short noncoding RNAs and minimizing cancer progression (Peng, Theng, et al., 2021). It has been reported that proliferation, metastasis, and drug resistance feature of tumor cells are affected by miRNAs (Ashrafizadeh, Zarrabi, et al., 2020; Gao, Shen, et al., 2020; Niu, Yang, et al., 2021; Tormo, Ballester, et al., 2019). The upregulation of tumor-promoting miRNAs such as miRNA-4262 in cancers can mediate PTX resistance via PTEN downregulation and subsequent PI3K/Akt signaling activation (Sun, Zhou, et al., 2019). Furthermore, miRNAs are valuable sources for tumor diagnosis and prognosis in pre-clinical and clinical studies (Bayarmaa, Wu, et al., 2019; Leidinger, Hart, et al., 2016; Maki, Sasaki, et al., 2014; Tan, Tan, et al., 2020). Consequently, improving our knowledge toward miRNAs and their expression profile in cancer can be beneficial in cancer therapy.

2.1.2 | PIWI-interacting RNAs

PIWI-interacting RNAs (piRNAs) are another member of RNA molecules with 26–31 nucleotides in length capable of binding to PIWI proteins (Dana, Mansournia, et al., 2020). In order to exert regulatory role, PIWI proteins and polycomb group proteins (PcGs) bind to PcG response elements in genome and these are tightly regulated by piRNAs (Lin, 2007). Overall, there are three distinct kinds of piRNAs including lncRNA-derived piRNAs, mRNA-derived piRNAs, and transposon-derived piRNAs. It has been reported that there are two subclusters for piRNAs including piRNAs acting on premeiotic germ cells (pre-pachytene piRNAs) and those working in meiosis and haploid spermatid phase (pachytene piRNAs). The molecular characteristics of these piRNAs are similar, and difference is that pre-pachytene piRNAs cluster contains repetitive sequence elements (Wei, Huang, et al., 2017). The piRNAs as small noncoding RNAs are associated with certain ARGONAUTE proteins of PIWI clade including MIWI, MILI, and MIWI2 in mouse, PRG-1 in *Caenorhabditis elegans*, and Argonaute 3 and Aubergine in Drosophila (Ramat & Simonelig, 2020). Two interconnected mechanisms including phasing and ping-pong amplification are involved in the production of piRNAs. Notably, these two mechanisms are physically separated in cells, so that phasing occurs in outer membrane of mitochondria, while ping-pong amplification occurs in Nuage comprising membraneless ribonucleoprotein granules localized at the periphery of germ cell nuclei (Ding, Liu, et al., 2019; Ge, Wang, et al., 2019; Huang, Gao, et al., 2011; Huang, Li, et al., 2014; Watanabe, Chuma, et al., 2011).

piRNAs are key players in physiological and pathological events due to their ability in regulating gene expression at transcriptional and post-transcriptional levels (Liu, Dou, et al., 2019). The dysregulation of piRNAs is an obvious finding in different cancers. For instance, in breast cancer, piRNA-36712 demonstrates decrease in expression and its overexpression impairs proliferation and invasion of tumors via combination with SEPW1P RNA (Tan, Mai, et al., 2019). A similar phenomenon occurs in gastric cancer; so piRNA-651 demonstrates an increase in expression to suppress apoptosis and promote cancer proliferation. Furthermore, this piRNA enhances cell cycle progression via inducing cyclin D1 and CDK4 expressions (Li, Luo, et al., 2016; Yao, Wang, et al., 2016). Noteworthy, piRNAs are potential regulators of the therapy response of tumors. piRNA-39980 reduces the sensitivity of neuroblastoma cells to doxorubicin chemotherapy via apoptosis inhibition (Roy, Das, et al., 2020).

2.1.3 | Small interfering RNAs

After the discovery of RNA interference (RNAi) in 1990s, this therapeutic tool obtained much attention in pre-clinical and clinical settings (Ashrafizadeh, Hushmandi, et al., 2020; Ashrafizadeh, Zarrabi, et al., 2020; FiBahreyni & Luo, 2020; Fire et al., 1998; Lee, Kim, et al., 2016; Mirzaei, Gholami, et al., 2021; Mirzaei, Gholami, et al., 2021; Mirzaei, Mahabady, et al., 2021). Small interfering RNA (siRNA) is double-stranded RNA with 21-25 nucleotides capable of silencing target genes (Kleinman, Kaneko, et al., 2012; Zamore, Tuschl, et al., 2000). The siRNA comprises two strands including sense (passenger) and antisense (guide) strands. These two strands

are attached to each other via a protein complex known as RNA-Induced Silencing Complex (RISC; Fakhr, Zare, et al., 2016; Parvani & Jackson, 2017). The task of guide strand is the identification of complementary mRNA and after its connection, RISC complex formed. Then, catalytic subunit of RISC, called argonaute 2 (Ago2) provides cleavage of target mRNA (Martinez, Patkaniowska, et al., 2002; Meister & Tuschl, 2004). As siRNAs can downregulate expressions of target genes, they are artificially synthesized in laboratory for targeting specific pathways involved in disease progression, particularly cancer. In field of cancer therapy, siRNAs significantly diminish the growth and invasion of tumors as well as enhance their sensitivity to therapy. However, off-targeting features and degradation by enzymes have limited siRNA potential in cancer therapy, leading to the development of delivery systems for enhancing its efficacy in gene silencing and cancer suppression (Ashrafizadeh, Delfi, et al., 2021; Ngamcherdtrakul & Yantasee, 2019, Subhan & Torchilin 2019; van den Brand, Mertens, et al., 2018; Yonezawa, Koide, et al., 2020). The use of siRNA in chemosensitivity demonstrates an increase, so that by disrupting cancer progression, inducing apoptosis, and reducing expression level of factors involved in cancer cell growth and invasion, siRNA can enhance the chemosensitivity of cancer cells (Butt, Amin, et al., 2016; Li, Tao, et al., 2017; Pan et al., 2020; Tian, Pan, et al., 2019; Wang, Song, et al., 2021; Wang, Xu, et al., 2018; Zhao, Xu, et al., 2017).

2.1.4 | Short-hairpin RNA

In the previous section, it was mentioned that siRNA has its own advantages and disadvantages. Some of these cons include off-targeting and enzyme degradation. In order to overcome these challenges, vectors generating short-hairpin RNA (shRNA) have been developed that can be processed into short duplex RNAs in cells, functioning similar to siRNA (Bernards, Brummelkamp, et al., 2006). This kind of gene silencing requires stabilization and incorporation of vector into host genome. Furthermore, it has been reported that hairpin cassette can be loaded into adenoviral, retroviral, and lentiviral vectors for targeted delivery of shRNA into various cell kinds (Brummelkamp, Bernards, et al., 2002; Dirac & Bernards, 2003; Khvorova, Reynolds, et al., 2003; Michiels, van Es, et al., 2002; Stegmeier, Hu, et al., 2005). After infecting and replicating in cells, nuclear shRNAs undergo expression to produce hairpin RNAs, and then, they translocate to cytoplasm. In the next step, Dicer enzyme involves in cleavage of shRNA and consequent production of siRNA. Upon incorporation of siRNA into RISC complex, the target homologous mRNA is affected and the perfect binding sequence leads to cleavage and downregulating target gene (Zhang, Ding, et al., 2016). Hence, it appears that shRNA works similarly to siRNA in gene silencing. To date, a variety of studies have applied shRNA in gene silencing and suppressing cancer progression. LncRNA HULC silencing by shRNA provides miRNA-377-5p upregulation, resulting in hepatocellular carcinoma suppression (Yan, Wei, et al., 2020). More importantly, shRNA is also beneficial in increasing chemosensitivity for cancer suppression (Archid, Zieker, et al., 2020; Cheng, Ke, et al., 2016; Li, Zhang, et al., 2017).

2.2 | Long-chain noncoding RNAs

2.2.1 | Long noncoding RNAs

LncRNAs are another kind of ncRNAs with a length of more than 200 nucleotides that play a significant role in human disease regulation (Cantile, Di Bonito, et al., 2021; Feng, Wu, et al., 2020; Mirzaei, Paskeh, et al., 2021; Paskeh et al., 2021). LncRNAs undergo transcription by RNA polymerase II due to lack of open reading frame. There are five types of lncRNAs including sense, antisense, bidirectional, intron, and intergenic regions (Laurent, Wahlestedt, et al., 2015; Zhang & Zhu, 2014). Noteworthy, lncRNAs have the capacity of downregulating the expression of miRNAs via sponging (Tsang, Au, et al., 2015; Zhang, Cao, et al., 2016). Besides, lncRNAs contribute to other main biological processes in cells including cell cycle regulation, transcription inhibition/induction, histone modification, chromatin remodeling, and gene imprinting (Akhade, Dighe, et al., 2016; Hadji, Boulanger, et al., 2016; Wu, Su, et al., 2016; Zhou, Zhang, et al., 2017). LncRNAs can function as decoys for sequestering transcription factors (Hung, Wang, et al., 2011). Although different lncRNAs possess various functions, it appears that most of the nuclear lncRNAs suppress transcription via directing chromatin modifiers to certain genomic loci and subsequent recruitment of DNA methyltransferases and histone modifiers (Davidovich & Cech, 2015; Tu, Yuan, et al., 2017). LncRNAs can modulate a wide variety of molecular mechanisms such as apoptosis, autophagy, proliferation, and migration (Kopp & Mendell, 2018; Nair, Chung, et al., 2020; Ransohoff, Wei, et al., 2018; Wong, Huang, et al., 2018). LncRNAs are key players in carcinogenesis, since they can modulate proliferation and metastasis of tumors. Furthermore, lncRNAs affect chemosensitivity of tumors (Jin, Ge, et al., 2020; Liang, Song, et al., 2020; Zhang, Wang, et al., 2020).

2.2.2 | Circular RNAs

In contrast to lncRNAs, circRNAs have a covalently closed loop structure lacking 5′caps and 3′poly-A tails and have obtained attention among other kinds of ncRNAs (Li, Jiang, et al., 2020; Zhang, Hu, et al., 2020). These new emerging ncRNAs were first discovered in viruses in 1970s (Sanger, Klotz, et al., 1976) and they are predominant transcripts of various human cell types (Salzman, Gawad, et al., 2012). To date, more than 25,000 circRNAs have been identified in human cells, and these stable and conserved products of RNA splicing are correlated with complementary ALU repeats in bordering introns (Jeck, Sorrentino, et al., 2013). The expression of circRNAs occurs in different eukaryotic cells, and it appears that their expression is cell-specific and also, developmental stage-specific (Jeck et al., 2013; Memczak, Jens, et al., 2013; Salzman,

Chen, et al., 2013; Salzman, Gawad, et al., 2012). The biogenesis process of circRNAs has not been fully understood, and different models have been proposed for their synthesis in cells. Specifically, four distinct models are considered as exon skipping, intron-pairing-driven circularization, ring-like intron formation pattern, and RNA-binding protein (RBP) formation (Liu, Guo, et al., 2020). On the other hand, there are three kinds of circRNAs such as ecircRNA, intron circRNA, and EIciRNA. A wide variety of circRNAs have been recognized to participate in cancer progression/inhibition. Proliferation, apoptosis, autophagy, metastasis, and drug resistance are influenced by circRNAs (Dou, Ren, et al., 2020; Han, Zhang, et al., 2020; Song, Hu, et al., 2020; Xie, Liang, et al., 2020). The present review focuses on revealing the role of circRNAs in PTX chemotherapy.

3 | MICRORNAs AND PACLITAXEL CHEMOTHERAPY

3.1 | Indirect effects

3.1.1 | miRNAs and cancer proliferation

The miRNAs with tumor-suppressor activity show a downregulation in expression in tumors (Ashrafizadeh, Ang, et al., 2020; Ashrafizadeh, Najafi, et al., 2020; Sailo, Banik, et al., 2019). Identification of these miRNAs and their upregulation can be advantageous in fight against tumors (Ashrafizadeh, Hushmandi, et al., 2020; Ashrafizadeh, Zarrabi, et al., 2020). miRNA-335 shows decreased expression level in triple-negative breast cancer cells and tissues, and increasing its expression is associated with the inhibition of proliferation, induction of apoptosis, and increased sensitivity to PTX chemotherapy (Hao, Lai, et al., 2019). miRNAs can synergistically cooperate together in cancer chemotherapy. In epithelial ovarian cancer cells, miRNA-874-3p and miRNA-874-5p jointly downregulated the expression of serine/threonine-protein kinase 2 (SIK2) to suppress cancer proliferation, leading to increased PTX sensitivity (Xia, Lin, et al., 2018). One of the most common functions of tumor-suppressing miRNAs is the regulation of apoptosis. miRNA-448 reduced the expression of Bcl-2 by binding to its 3′-UTR to trigger apoptosis and sensitize bladder cancer cells to PTX chemotherapy (Wang, Li, et al., 2018). A similar phenomenon occurs in non-small cell lung cancer cells, where miRNA-30a-5p reduced Bcl-2 expression and sensitized the cells to PTX-mediated apoptosis (Xu, Jin, et al., 2017). Therefore, miRNAs that suppress the proliferation and migration of cancer cells, can increase PTX sensitivity (Xiong, Yan, et al., 2018).

Increasing evidence suggests that tripartite motif-containing 27 (TRIM27) can promote cancer progression by Wnt signaling induction (Bhuvanalakshmi, Gamit, et al., 2018; Hwang et al., 2020; Liu, Tian, et al., 2020). TRIM27 stimulated p21 ubiquitination to prevent cell senescence and enhance breast cancer progression (Xing, Tang, et al., 2020). In ovarian cancer cells, miRNA-383-5p impaired proliferation via TRIM27 downregulation, resulting in increased PTX sensitivity (Jiang, Xie, et al., 2019). miRNAs can be targeted by antitumor compounds to enhance PTX sensitivity. Migration and proliferation of tumors can be suppressed by the natural compound morin (Nowak et al., 2020). Furthermore, this naturally occurring flavanol compound increased chemosensitivity via inhibition of autophagy (Pal Singh, Pal Khaket, et al., 2020). In prostate cancer cells, morin reduced miRNA-155 expression to induce the expression of GATA binding protein 3 (GATA3), leading to PTX sensitivity (Li, Jin, et al., 2017). The downregulation of tumor-suppressor miRNAs paves the way for increased expression of oncogenes and PTX resistance. miRNA-194-5p shows a decrease in expression in PTX-resistant ovarian cancer cells. Enhancing miRNA-194-5p expression was correlated with MDM2 inhibition, p21 upregulation, and stimulated G1 phase arrest (Nakamura, Sawada, et al., 2019).

Inhibition of tumor cell proliferation is the most important pathway, by which miRNAs can increase PTX sensitivity. miRNA-34a reduces cyclin D1 expression to enhance PTX sensitivity in breast cancer cells (Irani, Paknejad, et al., 2020). E2F1 and cyclin D1 can be simultaneously affected to increase tumor suppressor activity. E2F1 upregulation is in favor of enhancing tumor progression (Han, Zhao, et al., 2020; Zhao, 2020). miRNA-93 downregulated cyclin D1 and E2F1 to inhibit the activation of downstream target Akt and increase the PTX sensitivity in breast cancer cells (Bao, Chen, et al., 2020). Downregulation of cyclin-dependent kinase 6 (CDK6) and specificity protein 1 (Sp1) by miRNA-145 stimulated G1 phase arrest, leading to increased PTX sensitivity in ovarian cancer cells (Zhu, Li, et al., 2014). Furthermore, p53 inhibition by miRNA-193a-5p triggered apoptotic cell death in breast tumor and increased cytotoxicity of PTX (Khordadmehr, Shahbazi, et al., 2020). Upregulation of survivin (an anti-apoptotic protein) prevents apoptosis in cancer cells. miRNA-542-3p overexpression reduced survivin to disrupt the HER3/PI3K/Akt axis, leading to increased PTX sensitivity in breast cancer cells (Lyu, Wang, et al., 2018).

On the other hand, some miRNAs act as tumor-promoting factors that can promote cell growth and metastasis, and increase the PTX resistance of tumors. Although the exact role of miRNA-205-5p in cancer is not completely understood, it was reported that downregulation of miRNA-205-5p by lncRNA MEG32 led to cancer progression (Tao, Yang, et al., 2020), while its overexpression suppressed cancer proliferation and metastasis, and prevented drug resistance (Wang, Song, et al., 2020; Zhu, Shan, et al., 2020). In endometrial cancer cells, miRNA-205-5p increased PTX resistance by increasing proliferation and inhibiting apoptosis. Mechanistically, miRNA-205-5p diminished the expression of forkhead box protein O1 (FOXO1) to increase PTX resistance. Restoring FOXO1 expression was correlated with increased PTX sensitivity, along with impaired growth and more apoptosis (Lu, Xu, et al., 2019).

3.1.2 | miRNAs and cancer metastasis

IRAK1 is a serine/threonine kinase that participates in the immune system by regulating toll-like receptor signaling and interleukin-1

(Wee, Yatim, et al., 2015). IRAK1 can promote stemness and tumor growth to increase PTX resistance (Cheng, Lau, et al., 2018). Furthermore, downregulation of IRAK1 using ginsenoside (a plant sterol from ginseng) leads to enhanced PTX sensitivity in cancer cells (Wang, Song, et al., 2020). miRNA-146a diminished the proliferation and metastasis of breast tumors via IRAK1 inhibition, leading to enhanced PTX sensitivity (Liu, Yang, et al., 2020).

The integrin beta-1 (ITGB1) is a newly emerged oncogene in cancer, whose inhibition resulted in the inhibition of metastasis (epithelial-to-mesenchymal [EMT]) and angiogenesis (Tao, Yang, et al., 2020). ITGB1 downregulation enhances the antitumor activity of chemotherapeutic drugs in cancer therapy (Wang, Song, et al., 2020). ITGB1 is a target of some miRNAs, and ITGB1 upregulation disrupts the antitumor activity of miRNAs (Zhao, 2020). miRNA-29c reduced ITGB1 expression to disrupt the progression of nasopharyngeal cancer, and increased PTX sensitivity. Silencing miRNA-29c induced resistance to PTX chemotherapy (Huang, Hu, et al., 2019).

One possible route to transport miRNAs into cells is using exosomes. Exosomes are extracellular lipid bilayer microvesicles with 40–100 nm in size, and can contain RNA, DNA, and protein molecules derived from their cells of origin as cargoes (Colombo, Raposo, et al., 2014). Exosomes can participate in cancer progression and chemoresistance (Meehan & Vella, 2016; Sousa, Lima, et al., 2015; Syn, Wang, et al., 2016; Wee, Syn, et al., 2019). On the other hand, EMT transition is also a mediator of drug resistance (Lin, Ren, et al., 2020). Exposing gastric cancer cells to PTX was combined with the exosomal delivery of miRNA-155-5p to the cells. Then, EMT was activated and molecular pathways participating in the malignant phenotype of gastric tumor including GATA3 and TP53INP1 underwent upregulation, resulting in increased PTX resistance (Wee, Syn, et al., 2019). miRNAs participate in PTX resistance by enhancing the growth and metastasis of tumors (Huh, Kim, et al., 2013). EMT induces metastasis of tumor cells and can involve in drug resistance (Dai, Ahn, et al., 2016; Lee, Chinnathambi, et al., 2019; Tan, Sun, et al., 2020; Yang, Lee, et al., 2019). miRNA-181a stimulates EMT in mediating PTX resistance in ovarian tumors (Li, Xu, et al., 2016).

3.2 | Direct effects

3.2.1 | miRNAs and drug transporters

miRNA-199a is considered a promising target in PTX chemotherapy. Linc00518 downregulated miRNA-199a expression and enhanced multidrug resistance-associated protein 1 (MRP1) to increase PTX resistance (Chang, Hu, et al., 2018). In prostate cancer cells, miRNA-199a increased PTX sensitivity by reducing Yamaguchi sarcoma viral homolog 1 (YES1; Chen, Cao, et al., 2018). It was previously found that upregulation of both Bcl-2 and MRP1 increased PTX resistance. miRNA-7 impaired breast tumor progression and increased PTX sensitivity by suppressing Bcl-2 and MRP1 (Hong, Ding, et al., 2019).

3.2.2 | miRNAs and STAT3 signaling

The downstream targets of miRNAs are also important in PTX sensitivity. STAT3 is a tumor-promoting factor capable of mediating PTX resistance (Ashrafizadeh, Ahmadi, et al., 2019; Cong, Cui, et al., 2020; Kim, Cho, et al., 2014; Lee, Chiang, et al., 2014; Lee, Mohan, et al., 2020). Reducing the expression of STAT3 sensitized cancer cells to apoptosis and promoted the effects of PTX (Hindupur, Schmid, et al., 2020; Lee, Kim, et al., 2018; Mohan, Rangappa, et al., 2020). miRNA-125a enhanced apoptotic cell death in cervical tumor by STAT3 inhibition and increased PTX sensitivity (Zhang, Cao, et al., 2016). A similar finding in NSCLC showed that miRNA-9600 reduced protein levels of STAT3, without affecting the mRNA levels, resulting in cell cycle arrest, inhibition of migration, apoptosis stimulation, and increased PTX sensitivity (Sun, Li, et al., 2016). These two studies clearly demonstrate that STAT3 inhibition by miRNAs is of importance in PTX sensitivity via mediating apoptosis.

3.2.3 | miRNAs and c-Myc signaling

The c-Myc signaling pathway can increase cancer progression and induce PTX resistance. Inhibition of c-Myc can significantly promote PTX sensitivity (Lei, Hu, et al., 2020). Antitumor compounds such as silibinin can impair cancer proliferation, and trigger a cellular energy crisis via regulating c-Myc signaling (Iqbal, Chattopadhyay, et al., 2020). Increasing the expression of miRNA-4282 is correlated with induction of apoptosis and inhibition of migration. Furthermore, miRNA-4282 increased the PTX sensitivity of breast cancer cells by c-Myc downregulation (Zhao & Jiang, 2018). Therefore, it seems that c-Myc signaling is able to modulate miRNA expression in PTX sensitivity. This is in contrast to the aforementioned experiment which showed that c-Myc overexpression could induce PTX resistance. c-Myc activation elevates levels of miRNA-203b-3p and miRNA-203a-3p. These miRNAs induce apoptosis by binding to the 3′-UTR of the mRNA of the anti-apoptotic protein Bcl-xl, and reducing its expression, leading to PTX sensitivity (Aakko, Straume, et al., 2019). These studies demonstrate that downstream targets of miRNAs can form a feedback loop to regulate the response of cancer cells to PTX chemotherapy.

3.2.4 | miRNAs and MyD88 signaling

The role of MyD88 in carcinogenesis is well known. MyD88 downregulation using TJ-M2010-2 (a small molecule inhibitor of MyD88) significantly diminished proliferation, viability, and metastasis in breast cancer cells (Liu, Chen, et al., 2020). Noteworthy, inhibiting MyD88 was related to a decrease in the stemness of tumors and increased their sensitivity to chemotherapy (Chen, Luo, et al., 2020). MyD88 downregulation by miRNA-155-3p impaired breast cancer progression and promoted sensitivity to PTX chemotherapy (Zhang, Chen, et al., 2019).

3.2.5 | miRNAs and PDCD4 signaling

PDCD4 is a new emerging target in cancer therapy. PDCD4 downregulation is associated with cancer progression, which can be mediated by upstream mediators such as STAT3 and miRNA-155 (Wang, Song, et al., 2020; Xia & Zhao, 2020). The expression of miRNA-21-5p was increased in breast cancer cells and tissues. This tumor-promoting miRNA stimulated cell cycle progression and inhibited apoptosis in tumors via PDCD4 downregulation, leading to increased PTX resistance (Tao, Wu, et al., 2019).

3.2.6 | miRNAs and tumor microenvironment

Cancer-associated fibroblasts (CAFs) are stromal cells within the tumor microenvironment, which play a role in carcinogenesis and tumor progression (Crawford, Kasman, et al., 2009; Ligorio, Sil, et al., 2019). CAFs can participate in cancer progression by activating signaling pathways or tumor-promoting factors (Klemm & Joyce, 2015; Riaz, Havel, et al., 2017). On the other hand, ferroptosis is a new kind of programmed cell death mediated by iron-dependent lipid peroxidation and reactive oxygen species (ROS) production (Stockwell, Friedmann Angeli, et al., 2017). Ferroptosis inhibition can decrease the chemosensitivity of cancer cells. It has been reported that CAFs secrete miRNA-522 as a tumor-promoting factor, which in turn reduces PDCD4 activity to prevent ferroptosis induction via decreasing lipid peroxidation. It appears that PTX causes the secretion of miRNA-522 from CAFs via activating ubiquitin-specific protease 7 (USP7) to stabilize the heterogeneous nuclear ribonucleoprotein A1 (hnRNPA1; Zang, Li, et al., 2020). This interesting study suggested that the components in the tumor microenvironment could activate a complicated signaling pathway involved in PTX resistance.

The downregulation of tumor-promoting miRNAs sensitizes cancer cells to apoptotic cell death and impairs their proliferation, and can be responsible for increasing PTX sensitivity (Song, Zhang, et al., 2020). Different conditions can stimulate the upregulation of tumor-promoting miRNAs to increase PTX resistance. The tumor microenvironment is well known to show hypoxia resulting from a poor supply of oxygen to the rapidly proliferating cancer cells. Hypoxia can trigger the activation of molecular pathways, such as hypoxia-inducible factor-1α (HIF-1α) that can stimulate angiogenesis to increase oxygen and nutrients (Chen, Luo, et al., 2020; Cong, Cui, et al., 2020; Wang, Wang, et al., 2020). It has been reported that the expression of some miRNAs is altered in tumor hypoxia (Su, Liao, et al., 2020). It has been shown that miRNA-21 can induce PTX resistance via HIF-1α upregulation, further confirming the role of this molecular pathway in chemoresistance (Xie, Cao, et al., 2013). Hypoxia enhanced the expression of miRNA-27a in ovarian cancer cells resulting in reduced expression of apoptotic protease activating factor 1 (APAF1), and leading to PTX resistance (Feng, Shen, et al., 2020).

3.2.7 | miRNAs and other molecular pathways

Dicer is an RNA-binding protein that can regulate the expression of genes at posttranscriptional level by participating in the biogenesis of miRNAs (Theotoki, Pantazopoulou, et al., 2020). Dicer plays the role of a double-edged sword in cancer, and its activation has been shown to be involved in chemoresistance (Su, Hsu, et al., 2020). However, the story is different in PTX chemotherapy, where miRNA-18a decreased mRNA and protein levels of Dicer to trigger PTX resistance. Silencing miRNA-18a sensitized cancer cells to PTX-mediated apoptosis (Sha, Zhang, et al., 2016). Phosphatase and tensin homolog (PTEN) is an inhibitor of PI3K/Akt signaling, and reduces the proliferation and metastasis of cancer cells (Abadi, Zarrabi, et al., 2021; Ashrafizadeh, Zarrabi, et al., 2020). miRNA-21 inhibited PTEN signaling to trigger Akt phosphorylation, and promoted Bcl-2 and survivin expression to increase PTX resistance (Du, Cao, et al., 2017). PTX administration can directly affect the expression of some miRNAs in cancer therapy. For instance, upon PTX administration, the expression of tumor-promoting miRNA-143 was decreased to inhibit bladder cancer progression (Papadopoulos, Scorilas, et al., 2015). However, sometimes PTX administration enhances the expression of tumor-promoting miRNAs, which should be considered in PTX resistance. Table 1 and Figure 1 provide an overview of miRNAs regulating molecular pathways and mechanisms in PTX chemotherapy.

4 | PIWI-INTERACTING RNAs

To date, just one experiment has evaluated the role of piRNAs in PTX chemotherapy, indicating that there is still a long way in revealing the roles of these ncRNAs in PTX progression/inhibition. This experiment has focused on piRNA-36712 as a tumor-suppressing factor, so that its expression undergoes downregulation in breast cancer cells and tissues, and this low expression provides poor clinical outcomes. Upon piRNA-36712 downregulation, an increase occurs in expression level of SEPW1, as downstream target of this piRNA. Then, SEPW1 increases Slug expression, while it decreases expression levels of p21 and E-cadherin, leading to elevated growth and metastasis of breast tumor cells. piRNA-36712 is capable of downregulating SEPW1 expression via providing competition of SEPW1 mRNA with SEPW1P RNA for miRNA-7 and miRNA-324. SEPW1 inhibition by pi-36712 synergistically increases the potential of PTX in breast cancer eradication (Tan, Mai, et al., 2019).

5 | SMALL INTERFERING RNAs

After the discovery of siRNA, it was extensively applied in the field of cancer therapy and suppressing the progression of malignant cells via downregulating tumor-promoting factors. Then, it was found that combination of siRNA and chemotherapeutic agents can promote the sensitivity of cancer cells to chemotherapy (Chen, Zhang, et al., 2017; Wang, Zhao, et al., 2017; Yang, Meng, et al., 2018). Such strategy has

TABLE 1 miRNAs regulate response of cancer cells to PTX chemotherapy

miRNA	Cancer type	Effect on paclitaxel chemotherapy	Results	References
miRNA-26b	Gastric cancer	Sensitivity	Reduced CDC6 expression Suppressed cancer proliferation and invasion Apoptosis induction	Zhao, Zhang, et al. (2019)
miRNA-34c	Gastric cancer	Sensitivity	E2F1 inhibition enhanced miRNA-34c expression Apoptosis induction and impaired cancer cell proliferation	Liu, Tian, et al. (2020)
miRNA-150	Ovarian cancer	Sensitivity	Impaired cancer cell growth Triggered apoptosis Suppressed angiogenesis Notch3 downregulating and inhibition of downstream targets, Bcl-2, Bcl-W, cyclin D3, pS6, and NF-κB	Kim, Jeong, et al. (2017)
miRNA-134	Ovarian cancer	Sensitivity	Impaired malignancy and increased drug sensitivity	Zhu, Yang, et al. (2016)
miRNA-200c	Ovarian cancer	Sensitivity	Increased anoikis and adherence Reduced tumor formation Increased PTX sensitivity	Cittelly, Dimitrova, et al. (2012)
miRNA-134	Ovarian cancer	Sensitivity	Upregulated Pak2 expression Induced Bad phosphorylation at Ser112 and Ser136 Triggered apoptosis	Shuang, Wang, et al. (2015)
miRNA-193b-p	Ovarian carcinoma	Sensitivity	Downregulated PAK3 expression Suppressed cancer proliferation Reversed PTX resistance	Zhang, Qin, et al. (2017)
miRNA-107	Breast cancer	Sensitivity	Apoptosis induction Reduced cell viability and growth Downregulating Wnt1, β-catenin, and cyclin D1	Wang, Ma, et al. (2019)
miRNA-26a	Breast cancer	Sensitivity	Decreased cell proliferation Prevented colony formation Migration inhibition Apoptosis induction Mcl-1 downregulation	Gao, Li, et al. (2013)
miRNA-451	Breast cancer	Sensitivity	Suppressed cancer cell growth and migration Apoptosis stimulation Triggered cell cycle arrest Downregulated YWHAZ expression	Wang et al. (2017)
miRNA-30e	Breast cancer	Sensitivity	Inhibited tumor growth via downregulating Akt and ERK1/2 pathways Suppressed migration and metastasis of cancer cells Downregulated expression of IRS1 and HIF-1α	Liu, Li, et al. (2017)

TABLE 1 (Continued)

miRNA	Cancer type	Effect on paclitaxel chemotherapy	Results	References
miRNA-153-5p	Breast cancer	Sensitivity	Downregulated CDK1, Akt, and cyclin B1 Triggered cell cycle arrest in G2/M phase	Wang, Wu, et al. (2020)
miRNA-155-3p	Breast cancer	Sensitivity	Apoptosis induction Induced cell cycle arrest in G0/G1 phase Disrupted cancer metastasis Upregulated MYD88 and TP53INP1	Wang, Yan, et al. (2018)
miRNA-125b	Breast cancer	Sensitivity	Inhibited EMT Sema4C downregulation Reversed PTX resistance	Yang, Wang, et al. (2015)
miRNA-451	Breast cancer	Sensitivity	Reduced Bcl-2 at mRNA and protein levels Caspase-3 upregulation Apoptosis induction	Gu, Li, et al. (2015)
miRNA-34a	Cervical cancer	Sensitivity	Combination therapy with miRNA-34a, PTX, and microbubbles Reduced cancer proliferation Decreased microvessel density Downregulated Bcl-2 and CDK6	Yu, Zhao, et al. (2020)
miRNA-16	Lung cancer	Sensitivity	Caspase-3 activation	Chatterjee, Chattopadhyay, et al. (2015)
miRNA-17			Apoptosis induction Reversed PTX resistance	
miRNA-186	Lung cancer	Sensitivity	P53 upregulation and subsequent apoptosis	Ye, Zhang, et al. (2016)
miRNA-195	Non-small cell lung cancer	Sensitivity	CHEK1 downregulation Reversed PTX resistance	Yu, Zhang, et al. (2018)
miRNA-422a	Osteosarcoma	Sensitivity	Apoptosis stimulation Downregulated TGF-β2 and downstream targets Smad2 and Smad3	Liu, Xiusheng, et al. (2016)
miRNA-203	Colorectal cancer	Sensitivity	Downregulated SIK2 by binding to its 3′-UTR	Liu, Gao, et al. (2016)
miRNA-34a	Prostate cancer	Sensitivity	Reduced expression levels of SIRT1, HuR, and Bcl-2 Reversed PTX resistance	Kojima, Fujita, et al. (2010)
miRNA-493-3p	Breast cancer Ovarian cancer	Resistance	Downregulated Mad2 expression by binding to the 3′-UTR Triggered premature mitotic exit Increased aneuploidy Induced cellular senescence Associated with poor prognosis in cancer patients	Tambe, Pruikkonen, et al. (2016)

(Continues)

TABLE 1 (Continued)

miRNA	Cancer type	Effect on paclitaxel chemotherapy	Results	References
miRNA-520h	Breast cancer	Resistance	Protected cells against PTX-induced apoptosis	Su, Wang, et al. (2016)
			Downregulated DAPK2 expression	
			Associated with lymph node metastasis in patients	
miRNA-18a	Triple-negative breast cancer	Resistance	Induced autophagy as a pro-survival mechanism	Fan, Dai, et al. (2016)
			Downregulated mTOR signaling	
miRNA-590-5p	Gastric cancer	Resistance	Increased tumor size and lymph node metastasis	Shen, Yu, et al. (2016)
			Correlated with poor prognosis	
			Increased cancer cell proliferation and migration	
			Activated STAT3 and Akt/ERK pathways	
miRNA-4262	Non-small cell lung cancer	Resistance	Increased cell survival and invasion	Sun, Zhou, et al. (2019)
			Induced PI3K/Akt signaling via PTEN downregulation	
			Triggered PTX resistance	
miRNA-935	Non-small cell lung cancer	Resistance	Reduced SOX7 expression by binding to its 3′-UTR	Peng, Li, et al. (2018)
			Increased cell growth	
			Apoptosis inhibition	
			Increased Bcl-2 and Akt levels	
miRNA-29a	Colorectal cancer	Resistance	Overexpression of miRNA-29a in PTX-resistant cancer cells	Yuan, Li, et al. (2018)
			Downregulated PTEN expression	
			Activated Akt signaling	
			Promoted proliferation	
miRNA-140-3p	Chordoma	Resistance	Reduced PTEN expression	Zhao, Li, et al. (2019)
miRNA-155-5p			Triggered PI3K/Akt/mTOR signaling	
miRNA-363	Ovarian cancer	Resistance	Inhibited LATS2 expression	Mohamed, Hassan, et al. (2018)
			Decreased PTX sensitivity	

been applied in PTX sensitivity. Notch3 is a potential therapeutic target for inhibiting the proliferation and viability of cancer cells (Yen, Fischer, et al., 2015), where its overexpression occurs in PTX resistant-cancer cells, and its inhibition enhances apoptosis in ovarian cancer cells (Rahman, Nakayama, et al., 2012). Notch3 inhibition by siRNA significantly suppresses proliferation, invasion, and sphere-formation capacity of ovarian cancer cells. It has been reported that Nothc3-siRNA is efficient in enhancing PTX-mediated apoptosis and cell cycle arrest (G2/M phase) in chemoresistant-ovarian cancer cells (Kang, Jeong, et al., 2016). However, most of the studies have focused on developing nanocarriers for delivery of siRNA in PTX sensitivity. This is due to degradation of siRNA by RNase enzymes and also, off-targeting feature, minimizing efficiency of siRNA when it is applied in vivo. Therefore, the utilization of siRNA for cancer treatment in clinical course requires further progress to improve its potential. For this reason, scientists have focused on developing nanostructures for protecting siRNA against degradation, enhancing its intracellular accumulation, minimizing its off-targeting feature, increasing its efficiency in gene silencing, and finally, providing PTX sensitivity (Büyükköroğlu, Şenel, et al., 2019; Byeon, Lee, et al., 2018; Liu, Lo, et al., 2019; Liu, Long, et al., 2020; Michael, Lam,

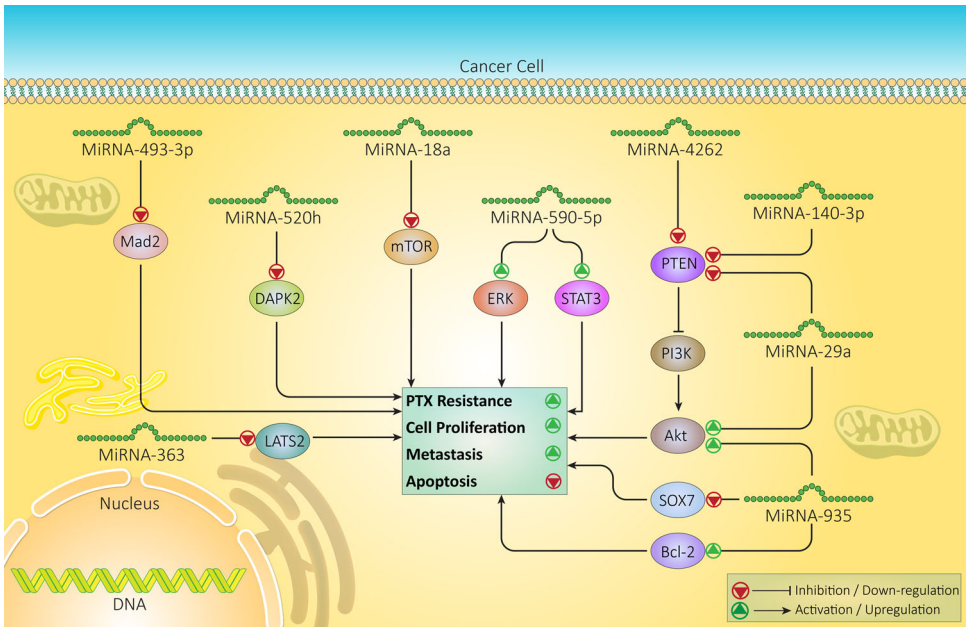

FIGURE 1 Response of cancer cells to PTX chemotherapy is regulated by miRNAs. Molecular pathways including mTOR, Mad2, STAT3, ERK, and SOX7 are among those affected by miRNAs. Furthermore, in modulating response to PTX chemotherapy, proliferation, and invasion of cancer cells are influenced by miRNAs

et al., 2020; Wang, Yan, et al., 2019; Yang, Zhang, et al., 2020; Yu, Bi, et al., 2019; Zhang, Zhao, et al., 2020; Zhu, Yang, et al., 2017). Thanks to the efforts performed in providing siRNA delivery towards PTX sensitivity, to date, a variety of nanoarchitectures have been designed for siRNA delivery. Recently, PTX- and E7-siRNA-loaded polymeric nanocarriers have been developed for synergistic chemotherapy of cervical cancer. The benefit of this study is that both in vitro and in vivo experiments were performed to show their efficacy. In HeLa cells, these nanostructures enhance PTX sensitivity via suppressing Akt signaling. In vivo experiment demonstrates an increase in tumor accumulation (up to threefold increase) and promoted immune escape ability that can suppress tumor growth up to 83.6% (Xu, Liu, et al., 2020). As cervical cancer is a leading cause of death in women, vaginal nanoformulations for co-delivery of PTX and Bcl-2-siRNA have been developed. The resulting solid lipid nanoparticles (SLNs) have zeta potential of 22–48 mV, showing their stability and also, particle size of 180 nm is of importance for penetration into cancer cells. By downregulating Bcl-2 as an anti-apoptotic factor, SLNs remarkably promote PTX sensitivity of cervical cancer cells (Büyükköroğlu, Şenel, et al., 2016). It is worth mentioning that two siRNAs can also be loaded on nanocarriers for potentiating antitumor activity of PTX. In fact, due to progress in the field of molecular biology and genetics, tumor-promoting factors involved in PTX resistance have been identified, and the next step is for bioengineers to develop effective nanocarriers. The MDR1-siRNA- and Bcl-2-siRNA-loaded polymeric nanoparticles can dually down-regulate expression levels of MDR1 and Bcl-2 as factors involved in chemoresistance to enhance PTX sensitivity of ovarian cancer cells (Risnayanti, Jang, et al., 2018). The distinct properties of tumor microenvironment such as mild acidic pH can be employed for developing stimuli-responsive nanoparticles in siRNA delivery. An experiment has prepared pH-sensitive polymeric nanostructures for co-delivery of PTX and survivin-siRNA in lung tumor therapy. The release of drug and siRNA from these nanocarriers occurs at pH 5.5 which is similar to pH of tumor microenvironment. Exposure of A549 cells to these nanostructures suppresses their proliferation and increases cellular uptake of both PTX and siRNA. Tumor proliferation inhibition and increased survival of mice occur using PTX- and survivin-siRNA-loaded polymeric nanostructures (Jin, Jin, et al., 2018). Overall, the following points can be concluded from these studies:

1) siRNA is a potential tool in reversing PTX resistance enhancing PTX-mediated apoptosis and cell cycle arrest in cancer cells via downregulating tumor-promoting factors,
2) The synergistic impact between siRNA and PTX has made this combination an appropriate strategy in cancer chemotherapy,
3) In order to elevate efficiency of siRNA in gene silencing and chemosensitivity, different nanocarriers have been developed for co-delivery of siRNA and PTX, and
4) More progress should be made in evaluating biocompatibility of siRNA- and PTX-loaded nanostructure to make them appropriate for clinical trials (Table 2 and Figure 2).

6 | SHORT-HAIRPIN RNAs

With respect to the potential of shRNA in silencing tumor-promoting factors, this strategy is beneficial in impairing progression of cancer cell, and enhancing their sensitivity to PTX chemotherapy. Multidrug

TABLE 2 Application of siRNA for promoting PTX sensitivity in cancer treatment

siRNA	Cancer type	Delivery method	Remarks	References
Bcl-2	Melanoma	Liposome	Smart nanoparticles sensitive to pH	Reddy, Garikapati, et al. (2016)
			Exerting synergistic impact	
			Decreasing cancer proliferation and survival	
			Efficacy in vitro and in vivo	
Interleukine-1α	Colon adenocarcinoma	Polymeric nanoparticles	Combination cancer therapy	Ou, Byeon, et al. (2019)
			Particle size less than 200 nm	
			Selective targeting of cancer cells via phrin-A2 receptor-specific peptide modification of nanocarriers	
RelA	Prostate cancer	Gold nanoparticles	Stimulating efficient endosomal escape of siRNA	Luan, Rahme, et al. (2019)
			Downregulating RelA gene	
			Sustained systemic exposure	
			Downregulation of NF-κB signaling	
			Enhancing PTX sensitivity	
Survivin	Brain glioma	Cationic liposomes	Dual modification of liposomes with aptamer and low-density lipoprotein receptor-related protein for enhancing selectivity toward cancer cells	Sun, Chen, et al. (2018)
			Apoptosis induction	
			High cytotoxicity against cancer cells	
VEGF	Glioma	Polymeric nanoparticles	Enhancing cell distribution	Wen, Wen, et al. (2020)
			Receptor-mediated delivery into cells	
			Increasing apoptosis	
			Inhibiting neovascularization	
			Elevating PTX sensitivity	
MDR1	Breast cancer	Micelles	Particle size of 171.6 nm	Yang, Zhu, et al. (2017)
			Encapsulation efficiency as much as 93%	
			Specific targeting of cancer cells overexpressing LDL receptor	
			Protecting siRNA from degradation by macrophage phagocytosis	
			Downregulating MDR1 and P-gp expression levels	
			Increasing PTX sensitivity	
eIF4E	Breast cancer	Lipid nanoparticles	Intravenous administration results in gene silencing for at least 1 week	Gujrati, Vaidya, et al. (2016)
			pH-sensitive	
			Enhancing PTX sensitivity	
			Negligible side effects	

TABLE 2 (Continued)

siRNA	Cancer type	Delivery method	Remarks	References
Bcl-2	Breast cancer	Polymeric micelles	Caspase-3 cleavage Downregulating Bcl-2 expression Apoptosis induction Increasing PTX sensitivity	Lee, Lee, et al. (2017)
Survivin	Lung cancer	Nanobubble	SiRNA protection against degradation Enhancing its cellular uptake Apoptosis stimulation Exerting synergistic impact	Akbaba, Erel-Akbaba, et al. (2020)
TR3	Pancreatic cancer	Peptide-modified dendrimers	Redox-responsive Providing endosomal escape Preventing intracellular degradation Facilitating PTX and siRNA release Enhancing PTX sensitivity	Li, Wang, et al. (2017)

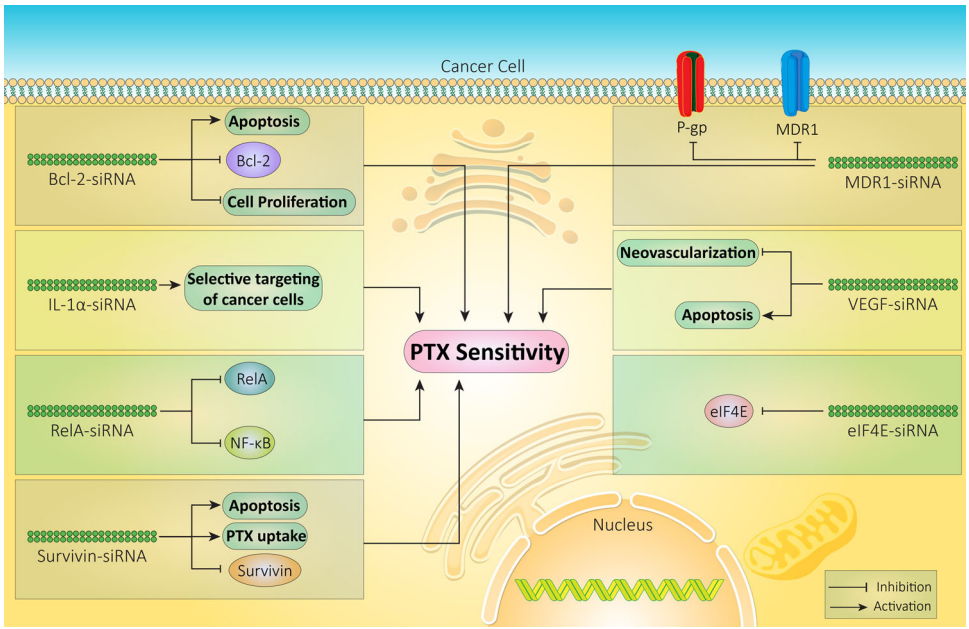

FIGURE 2 Application of siRNA in reversing PTX resistance via suppressing molecular pathways responsible for cancer progression

resistance 1 P-glycoprotein (MDR1) is responsible for inducing resistance of cancer cells to PTX chemotherapy via providing efflux of this chemotherapeutic agent (Fan, Zhu, et al., 2020; Kikuchi, Maishi, et al., 2020). Exposure of cancer cells to MDR1-shRNA is associated with an increase in their sensitivity to PTX chemotherapy, and in vivo experiment on mice demonstrates a significant decrease in tumor growth (Zhang, Wang, et al., 2012). It is worth mentioning that both mRNA and protein levels of target gene decrease upon shRNA transfection of cancer cells, resulting in PTX-mediated apoptosis and decrease in cell survival and proliferation (Jin, Xie, et al., 2014). More importantly, by downregulating an upstream mediator via shRNA, a signaling network that is responsible for cancer growth is disrupted, paving the way for chemosensitivity. It has been reported that transforming growth factor β-activated protein kinase 1 (TAK1)-binding protein 3 (TAB3) is a tumor-promoting factor and is vital for TAK1 activation in response to TNF-α or IL-1β. TAB3 inhibition by shRNA results in enhanced sensitivity of ovarian cancer cells via downregulating NF-κB signaling

(Chen, Wang, et al., 2016). In fact, TAB3 inhibition by shRNA paves the way for NF-κB downregulation and PTX sensitivity of cancer cells. Another experiment using shRNA screening also reveals the role of NF-κB signaling in PTX resistance (Lai, Fang, et al., 2020). In addition to NF-κB, Notch1 plays a significant role in PTX resistance of cancer cells. Notch1 overexpression in cancer patients (head and neck cancer) reduces response to PTX chemotherapy (Zhang, Zhou, et al., 2019). Notch1 downregulation is correlated with an increase in potential of PTX in cancer elimination via caspase-3 and -9 upregulation and Bcl-2 downregulation, resulting in apoptotic cell death (Zhou, Sun, et al., 2017). Exposing MCF-7 cells (breast cancer cells) to Notch1-shRNA promotes PTX-mediated cell death and impairs their proliferation and progression. It seems that upon Notch1 inhibition by shRNA, expression level of NF-κB as an anti-apoptotic factor undergoes downregulation that is responsible for increased PTX-mediated apoptosis (Mao, Song, et al., 2013). A similar phenomenon occurs after Akt2 inhibition. Colorectal cancer cells are capable of obtaining PTX resistance via upregulation Akt2 expression. Inhibiting Akt2 signaling via shRNA paves the way for downregulation of MDR1 and MRP1, leading to increased PTX-induced apoptosis (Ding, Xu, et al., 2015).

Although previous studies demonstrate the potential of shRNA in gene silencing and increasing PTX sensitivity, it appears that designing carriers for shRNA delivery can significantly enhance its intracellular accumulation and promote its efficacy in gene silencing. Such strategy has been developed and investigated by different studies to shed some light on shRNA-mediated delivery in potentiating cancer therapy and PTX sensitivity. To date, different kinds of nanoparticles have been developed for shRNA delivery (Chen, Fan, et al., 2020; Sánchez-Sarasúa, Ribes-Navarro, et al., 2021; Xu, Zhou, et al., 2020). Each of them has its own unique feature, but overall, they are beneficial in enhancing intracellular accumulation of shRNA and PTX, as well as promoting chemosensitivity. The upregulation of survivin is responsible for PTX resistance of ovarian cancer cells. To provide PTX sensitivity, an experiment has designed polymeric micelles containing survivin-shRNA and PTX. The PTX is embedded in core, while shRNA is attached to shell of micellar nanoparticles. By enhancing penetration of shRNA and PTX into cancer cells, a significant decrease occurs in expression levels of Bcl-2 and survivin, sensitizing ovarian cancer cells to PTX-mediated apoptosis (Hu, Li, et al., 2012). Another study has applied polymeric nanoparticles for survivin-shRNA delivery in lung cancer treatment. The efficient delivery of shRNA to nuclei of A549 cells, enhances efficacy of shRNA in gene silencing (survivin downregulation). Then, PTX effectively induces apoptosis and cell cycle arrest (G2/M phase) in lung cancer cells (Shen, Yin, et al., 2012). One of the important possibilities is the surface modification of nanocarriers for enhancing their selectivity toward cancer cells. The tripeptide arginine–glycine–aspartic sequence (RGD) can specifically bind to integrin αvβ3 (Murphy, Majeti, et al., 2008). Therefore, surface modification of nanoparticles with RGD promotes their entrance into cancer cells. The RGD-modified polymeric nanoparticles can enhance intracellular accumulation of survivin-shRNA in lung cancer cells, leading to their PTX sensitivity (Shen, Meng, et al., 2014). In addition to targeting proliferation of cancer cells, shRNA-loaded nanostructures can affect migration and invasion of cancer cells in providing PTX sensitivity. The Twist is an inducer of EMT, and its overexpression promotes cancer metastasis (Sonongbua, Siritungyong, et al., 2020; Wang, Liao, et al., 2020). It has been reported that Twist-shRNA- and PTX-loaded polymeric nanoparticles can downregulate the expression level of Twist at protein levels up to 91%, which is of importance in disrupting breast cancer invasion and increasing their PTX sensitivity (Shen, Sun, et al., 2013). Overall, the following conclusions can be made from shRNA in PTX chemotherapy:

1) The first step is identification of tumor-promoting factors and designing shRNA for downregulation and impairing cancer progression,
2) The shRNA can significantly enhance PTX sensitivity of cancer cells, and
3) In order to promote intracellular accumulation of shRNA and its efficacy in gene silencing as well as promoting potential in PTX sensitivity, delivery methods have been developed (Figure 3 and Table 3; Guo, Hong, et al., 2012; Long, Yin, et al., 2012; Zhou, Zhang, et al., 2018).

7 | LONG NONCODING RNAs

As mentioned above, the increased migration and proliferation of cancer cells is correlated with the development of chemoresistance (Manu, Shanmugam, et al., 2014; Manu, Shanmugam, et al., 2015). The lncRNA MAPT-AS1 was overexpressed in breast cancer cells and increased growth, viability, and invasion. This was mediated by upregulation of the tumor-promoting factor MAPK. MAPT-AS1 silencing was correlated with less cancer progression and increased sensitivity to PTX chemotherapy (Pan, Pan, et al., 2018). In contrast, tumor-suppressing lncRNAs, such as KB-1471A8.2 can enhance PTX sensitivity. The lncRNA KB-1471A8.2 induced cell cycle arrest in the G0/G1 phase and increased the PTX sensitivity in ovarian cancer cells (Zhang, Liu, et al., 2019). Some lncRNAs can affect molecular mechanisms with a role in chemosensitivity, such as autophagy (Wu, Liu, et al., 2020). Targeting upstream mediators to promote autophagy and increase PTX sensitivity is of importance (Deng, Shanmugam, et al., 2019; Singh, Vats, et al., 2018). The antisense intronic (Ai) lncRNA EGOT induced autophagy and promoted autophagosome formation via ITPR1 upregulation, leading to increased PTX sensitivity (Xu, Wang, et al., 2019). However, the dual role of autophagy in cancer cells should be considered. Although the above-mentioned study suggested that induction of autophagy could promote PTX sensitivity, there are other studies demonstrating that autophagy activation can actually stimulate PTX resistance (Wang, Liu, et al., 2020; Zhao, Wang, et al., 2021). This is due to fact that autophagy plays the role of a double-edged sword in cancer, and its exact role in each situation is not certain. Further studies will be required to shed more light on the regulation of autophagy by lncRNAs, and its impact on PTX chemotherapy.

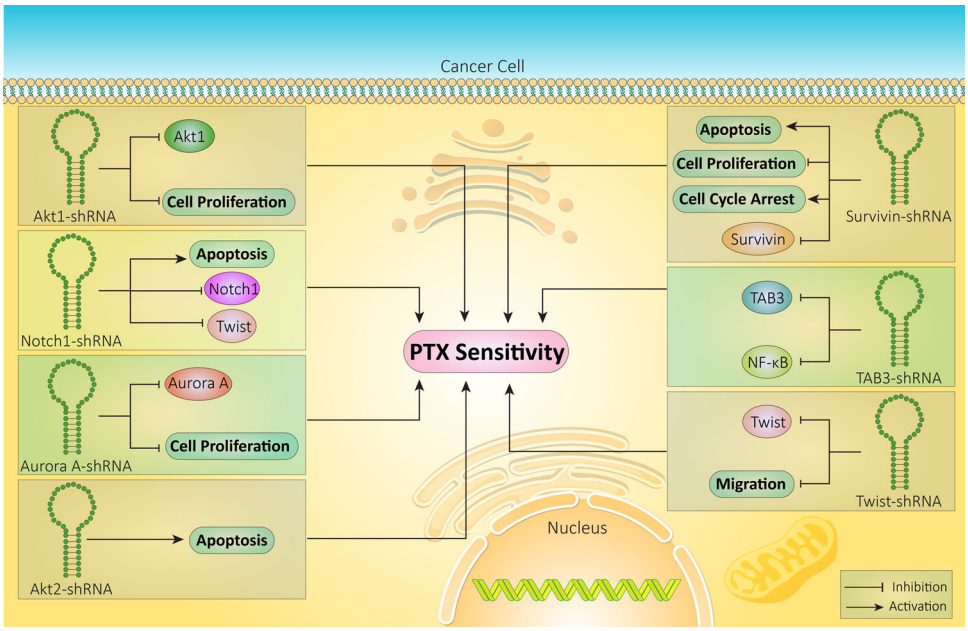

FIGURE 3 The application of shRNA in enhancing PTX sensitivity of cancer cells

Protein kinase B (Akt) is a potential target of lncRNAs in cancer cells. The lncRNA FER1L4 triggered apoptosis in osteosarcoma cells and impaired their viability and proliferation via Akt downregulation (Ye, Tian, et al., 2019). Furthermore, silencing of lncRNA XIST promoted miRNA-126 expression to suppress Akt signaling, leading to impairment of glucose metabolism and inhibition of proliferation (Cheng, Luo, et al., 2020). The lncRNA H19 reduced Akt expression to induce apoptosis in triple-negative breast cancer cells, resulting in increased PTX sensitivity (Han, Han, et al., 2018). The interaction between lncRNAs and miRNAs is important to predict the response of cancer cells to PTX chemotherapy (Jiang, Liu, et al., 2016). LncRNA H19 functions as a tumor-promoting factor in several cancer types. The positive association of H19 with miRNA-675 led to EMT induction and increased cancer progression (Peperstraete, Lecerf, et al., 2020). In addition to metastasis, H19 can enhance cancer proliferation and viability via p53 downregulation (Li, Ma, et al., 2020). LncRNA H19 downregulated miRNA-193a-3p expression to reduce the sensitivity of hepatocellular carcinoma cells to PTX chemotherapy (Ma, Yuan, et al., 2018). Some lncRNAs can regulate mitosis, for instance, lncRNA MA-linc1 can affect the cell cycle by reducing the number of cells in the G1 phase and increasing the number in the G2/M phase. The impact of MA-linc1 on the cell cycle is mediated via the inhibition of a neighboring gene, known as Purα that inhibits apoptosis in cancer cells, leading to increased PTX resistance (Bida, Gidoni, et al., 2015). The identification of lncRNAs capable of triggering apoptosis in cancer cells is of interest to increase PTX sensitivity (Zheng, Li, et al., 2020). Furthermore, lncRNAs can also regulate miRNAs which are involved in the regulation of cell cycle and apoptosis. LncRNA CCAT1 lowers the expression of miRNA-181a via sponging, to inhibit apoptosis in nasopharyngeal cancer cells, leading to PTX resistance (Wang, Zhang, et al., 2017). The lncRNA CCAT1 is a tumor promoter that is also involved in chemosensitivity. Silencing CCAT1 increased the sensitivity of prostate cancer cells to PTX chemotherapy via upregulating miRNA-24-3p (Wu, Liu, et al., 2020). Clinical studies have confirmed the role of lncRNAs in triggering PTX resistance. A clinical study evaluated 144 patients with breast cancer and demonstrated that single nucleotide polymorphisms in lncRNA MEG3 were correlated with a better response of cancer patients to PTX chemotherapy (Bayarmaa, Wu, et al., 2019). The identification of novel lncRNAs involved in PTX resistance can be accelerated by the use of next-generation deep sequencing (Ren, Li, et al., 2016).

An important function of lncRNAs in cancer is their ability to regulate the activity of drug efflux transporters. ATP-binding cassette (ABC) transporters are the best understood type of efflux transporters in cancer, and their upregulation by lncRNAs can lead to PTX resistance. One example of this was the lncRNA CTD-2589M5.4 (Ma, Yuan, et al., 2018). The methylation level of lncRNAs can determine the cancer response to PTX chemotherapy. Hypermethylation of lncRNA MEG3 reduced the PTX sensitivity of breast cancer cells, and the prevention of MEG3 methylation could be considered as a strategy to improve the response of breast cancer cells to PTX chemotherapy (Li, Wang, et al., 2020).

LncRNA MALAT1 is able to promote cancer proliferation via induction of autophagy and downregulation of miRNA-204 (Shao, Zhao, et al., 2020). The expression of MALAT1 was upregulated in ovarian cancer cells and was correlated with proliferation, migration, and cisplatin resistance (Wang et al., 2020). A similar result was observed in non-small lung cancer cells treated with PTX. In vitro and in vivo experiments showed that MALAT1 and miRNA-197-3p acted together to reduce p120 expression, thereby increasing proliferation and migration, as well as inducing PTX resistance (Yang, Li, et al., 2019). MALAT1 was overexpressed in laryngeal squamous cell

TABLE 3 The critical role of shRNA in enhancing PTX sensitivity of cancer cells

shRNA	Cancer type	Delivery method	Remarks	References
Survivin	Ovarian cancer	Micelles	downregulating survivin gene as an anti-apoptotic factor Impairing cancer progression Enhancing PTX sensitivity	Hu, Li, et al. (2012)
TAB3	Ovarian cancer	–	downregulating TAB3 expression and subsequent inhibition of NF-κB signaling Enhancing PTX sensitivity via impairing cancer progression and proliferation	Chen, Wang, et al. (2016)
Survivin	Lung cancer	Polymeric nanoparticles	Enhancing nuclei delivery of survivin-shRNA and enhancing its potential in gene silencing Promoting PTX-mediated apoptosis and cell cycle arrest (G2/M phase)	Shen, Yin, et al. (2012)
Survivn	Lung cancer	RGD-modified polymeric nanoparticles	Enhancing intracellular accumulation of cancer cells via RGD modification Reducing surivivn expression Elevating apoptotic cell death	Shen, Meng, et al. (2014)
Twist	Breast cancer	Polymeric nanostructures	Suppressing migration and invasion of cancer cells Inhibiting Twist expression Increasing penetration of PTX and shRNA in cancer cells Enhancing PTX sensitivity	Shen, Sun, et al. (2013)
Akt1	Breast cancer	Thermosensitive hydrogels	Exerting synergistic impact Suppressing cancer progression in vitro and in vivo Downregulating Akt1 expression Increasing PTX sensitivity	Guo, Hong, et al. (2012)
Notch1	Breast cancer	–	Downregulating Notch1 expression and subsequent inhibition of NF-κB signaling Sensitizing cancer cells to apoptosis Enhancing PTX sensitivity	Mao, Song, et al. (2013)
Aurora A	Breast cancer	Adenovirus	Reducing aurora A expression at mRNA and protein levels Disrupting cancer proliferation Increasing PTX sensitivity	Long, Yin, et al. (2012)
Akt2	Colorectal cancer	–	Suppressing viability and growth of cancer cells Increasing apoptotic cell death Promoting PTX-mediated cancer inhibition impact	Ding, Xu, et al. (2015)
Survivin	Esophageal squamous cell carcinoma	Lentivirus	Impairing growth of cancer cells Reducing their colony-formation capacity Suppressing invasion and migration Promoting PTX sensitivityp	Zhou, Zhang, et al. (2018)

carcinoma patients, where it prevented apoptosis, increased invasion, and led to PTX resistance (Yu, et al., 2020). It seems that downstream targets of lncRNAs are also involved in mediating PTX resistance. Mitogen-activated protein kinase (MAPK) overexpression was associated with poor prognosis and triggered drug resistance (Sato, Schoenfeld, et al., 2020). MAPK upregulation in hypoxic conditions is correlated with the resistance of cancer cells to chemotherapy (Lu et al., 2020). In PTX-resistant endometrial cancer cells, the lncRNA HEIH stimulated the MAPK signaling pathway to enhance cancer survival and growth, leading to PTX resistance. HEIH downregulation was correlated with the reversal of PTX resistance via MAPK inhibition (Guo et al., 2020). In contrast to HEIH, the lncRNA FER1L4 downregulated the MAPK signaling pathway to suppress the progression of ovarian cancer cells, leading to PTX sensitivity (Liu et al., 2018). The association of MAPK with PTX resistance can be attributed to its effects on other factors, such as Slug. It has been reported that lncRNA SNHG12 stimulated the MAPK/Slug axis to promote cancer progression, invasion, and proliferation, leading to PTX resistance (Wang, Chen, et al., 2017).

The regulation of EMT by lncRNAs leading to PTX resistance suggests this mechanism could be a potential target to reverse chemoresistance. In EMT, the epithelial marker E-cadherin is downregulated, while mesenchymal markers such as vimentin and N-cadherin are increased (Hwang et al., 2020; Ko, Nam, et al., 2018; Loh, Chai, et al., 2019). EMT activation leads to increased cancer stemness (Wilson, Weinberg, et al., 2020) and drug resistance (Galle, Thienpont, et al., 2020; Nilsson, Sun, et al., 2020). The lncRNA PVT1 reduced the expression of miRNA-195 in cervical cancer cells to stimulate EMT, resulting in PTX resistance (Shen, Cheng, et al., 2017). The overexpression of zinc finger E-box binding homeobox 1 (ZEB1) induced metastasis and invasion of cancer cells via EMT induction (Drápela, Bouchal, et al., 2020; Wu, Zhong, et al., 2020). Regulating the expression of ZEB1 can inhibit the migration and invasion of cancer cells. It was reported that lncRNA NEAT1 decreased miRNA-194 expression to stimulate ZEB1, resulting in PTX resistance (Liu, Li, et al., 2017). In addition to ZEB1, the Wnt/β-catenin signaling pathway can act as an upstream mediator of EMT in cancer cells (Zhang, Du, et al., 2020). The tumor-promoting factor lncRNA ZFAS1 enhanced the expression and activation of Wnt in gastric cancer cells to promote EMT and increase metastasis. down-regulation of ZFAS1 was correlated with a reduction in β-catenin expression, inhibition of gastric cancer metastasis, and increased PTX sensitivity (Xu, He, et al., 2018). These studies bolster the conclusion that several lncRNAs are determining factors in regulating the response of cancer cells to PTX chemotherapy (Figure 4 and Table 4; Chen, Shen, et al., 2020; Horita, Kurosaki, et al., 2019; Shen, Cheng, et al., 2017; Shi & Wang, 2018; Yang, Meng, et al., 2018).

8 | CIRCULAR RNAs

CircRNAs have been less well investigated in cancer, compared to miRNAs and lncRNAs. However, it is now clear that circRNAs play a significant role in cancer and can regulate the response of cancer cells to chemotherapy, including PTX chemotherapy. In this section, a mechanistic discussion of the role of circRNAs in PTX resistance/sensitivity is provided.

Metastasis and invasion of cancer cells can be enhanced by ZEB1, which also leads to PTX resistance. Furthermore, drug efflux transporters such as P-gp can increase PTX resistance by decreasing the intracellular accumulation of this drug in cancer cells.

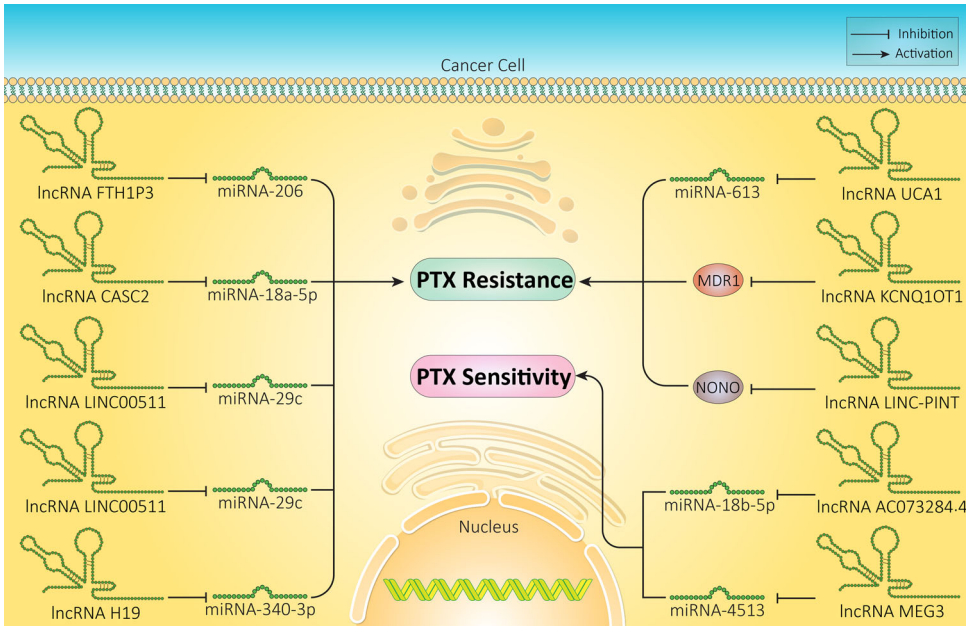

FIGURE 4 LncRNAs as key regulators of cancer response to PTX chemotherapy. Noteworthy, miRNAs are the most well-known downstream targets of lncRNAs

TABLE 4 Long noncoding RNAs as regulators of paclitaxel sensitivity and resistance

LncRNA	Cancer type	Effect on paclitaxel chemotherapy	Results	References
FTH1P3	Breast cancer	Resistance	Reduced miRNA-206 expression by acting as competing endogenous RNA Induced ABCB1 expression Enhanced cancer cell proliferation and cell cycle progression	Yang, Meng, et al. (2018)
AC073284.4	Breast cancer	Sensitivity	Reduced miRNA-18b-5p via sponging upregulated DOCK4 expression Suppressed EMT and metastasis	Wang et al. (2019)
CASC2	Breast cancer	Resistance	Induced CDK19 expression via miRNA-18a-5p inhibition Enhanced cancer progression and reduced PTX cytotoxicity	Zheng, Dong, et al. (2019)
MEG3	Breast cancer	Sensitivity	Apoptosis induction Inhibited cancer metastasis MiRNA-4513 inhibition Upregulated PBLD expression	Zhu, Wang, et al. (2020)
LINC00511	Breast cancer	Resistance	Downregulated miRNA-29c expression CDK6 upregulation Decreased cytotoxicity of PTX against cancer cells	Zhang, Zhao, et al. (2019)
H19	Breast cancer	Resistance	Enhanced metastasis of cancer cells via EMT induction MiRNA-340-3p sponging	Yan, Yang, et al. (2020)
H19	Breast cancer	Resistance	Inhibited cell apoptosis Inhibited transcription of BIK and NOXA	Si, Zang, et al. (2016)
NONHSAT141924	Breast cancer	Resistance	Increased cancer proliferation Enhanced cell survival Increased levels of CREB and Bcl-2	Zhu, Wang, et al. (2020)
UCA1	Breast cancer	Resistance	Reduced miRNA-613 via sponging CDK12 modulation Enhanced cancer progression	Liu, Jiang, et al. (2020)
LINC-PINT	Triple-negative breast cancer	Sensitivity	Degraded NONO in a proteasome-mediated manner Silencing of LINC-PINT enhanced PTX sensitivity	Yan, Yang, et al. (2020)
KCNQ1OT1	Lung cancer	Resistance	Enhanced expression of MDR1 Increased cancer malignancy Mediated PTX resistance	Ren, Xu, et al. (2017)
ENST00000500843	Lung adenocarcinoma	Sensitivity	Upregulation of this lncRNA promoted PTX sensitivity Sensitized cancer cells to apoptosis	Tian, Gao, et al. (2019)
CDKN2B-AS	Endometrial carcinoma	Resistance	Association with high pathological grade Low response to PTX chemotherapy MiRNA-125a-5p downregulation Enhanced expression of Bcl-2 and MRP4 as tumor-promoting factors	Shang, Ao, et al. (2019)

TABLE 4 (Continued)

LncRNA	Cancer type	Effect on paclitaxel chemotherapy	Results	References
LINC00672	Endometrial cancer	Sensitivity	Mediated p53-induced inhibition of LASP1 Suppressed cancer aggressive behavior Promoted PTX sensitivity	Li, Li, et al. (2017)
NEAT1	Endometrial carcinoma	Resistance	MiRNA-361 sponging Enhanced proliferation and invasion STAT3 upregulation	Dong, Xiong, et al. (2019)
Linc00518	Prostate cancer	Resistance	MiRNA-216-5p downregulation Triggered PTX resistance	He, Sun, et al. (2019)
SNHG6	Prostate cancer	Resistance	Sponging miRNA-186 Promoted cancer proliferation and invasion Induced PTX resistance	Cao, Sun, et al. (2020)
AFAP1-AS1	Prostate cancer	Resistance	Decreased expression levels of miRNA-195-5p Apoptosis inhibition	Leng, Liu, et al. (2020)
DANCR	Prostate cancer	Resistance	Reduced miRNA-135a expression Increased cancer cell proliferation Prevented apoptosis	Zhao, Zhang, et al. (2019)
PVT1	Gastric cancer	Resistance	Stimulated lymph node invasion Increased cancer malignancy Increased PTX resistance	Ding, Li, et al. (2014)
HOTAIR	Gastric cancer	Resistance	Downregulated miRNA-217 expression Enhanced cell proliferation, migration, and cell cycle progression Increased expression levels of GPC5 and PTPN14 Mediated PTX resistance	Wang, Qin, et al. (2018)
CRNDE	Colorectal cancer	Resistance	Reduced miRNA-126-5p expression Enhanced ATAD2 expression Increased cancer growth and PTX resistance	Leng, Liu, et al. (2020)
SNHG22	Ovarian carcinoma	Resistance	Affected miRNA-2467/Gal-1 axis Induced PI3K/Akt signaling Promoted ERK expression	Zhao et al. (2019)
SNHG5	Ovarian cancer	Sensitivity	Reduced miRNA-23a expression via sponging Impaired cancer proliferation Promoted PTX sensitivity	Lin, Shen, et al. (2020)
SNHG1	Ovarian cancer	Resistance	Reduced miRNA-216b-5p expression Prevented apoptosis Enhanced cancer cell viability and metastasis	Pei, Zhao, et al. (2020)

(Continues)

TABLE 4 (Continued)

LncRNA	Cancer type	Effect on paclitaxel chemotherapy	Results	References
UCA1	Ovarian cancer	Resistance	MiRNA-654-5p sponging SIK2 overexpression Enhanced cancer progression Mediated PTX resistance	Leng, Liu, et al. (2020)
UCA1	Ovarian cancer	Resistance	Regulated miRNA-129/ABCB1 axis Silencing of UCA1 enhanced PTX sensitivity	Wang, Ye, et al. (2018)
TUG1	Ovarian cancer	Resistance	Downregulated miRNA-29b-3p Induced pro-survival autophagy Reduced PTX cytotoxicity	Gu, Li, et al. (2020)
SDHAP1	Ovarian cancer	Resistance	MiRNA-4465 downregulation Increased expression of EIF4G2 Reduced apoptosis	Pei, Zhao, et al. (2020)
PRLB	Ovarian cancer	Resistance	Decreased cell apoptosis Reduced miRNA-150-5p expression Enhanced expressions of RSF1	Zhao and Hong (2020)
H19	Nasopharyngeal carcinoma	Resistance	Enhanced cancer proliferation and viability Reduced apoptosis Silencing of H19 increased PTX sensitivity	Fan, Zhu, et al. (2020)
TCL6	Renal cell carcinoma	Sensitivity	Downregulation of TCL6 was correlated with poor prognosis Reduced cell viability Promoted antitumor activity of PTX against cancer cells	Chen, Zhuang, et al. (2020)
SNHG7	Hypopharyngeal cancer	Resistance	Metformin administration reduced SNHG7 expression Metformin impaired proliferation and sensitized cells to PTX chemotherapy	Wu, Tang, et al. (2019)
PCAT1	Esophageal squamous cell carcinoma	Resistance	Reduced miRNA-326 expression Silencing of PCAT1 induced cell cycle arrest (G2/M phase), apoptosis, and PTX sensitivity	Huang, Wang, et al. (2019)

MiRNA-124-3p impairs cancer progression and increases PTX sensitivity via downregulation of ZEB1 and P-gp. The circ-PVT1 reduced miRNA-124-3 via sponging to increase PTX resistance in gastric cancer cells (Liu, Zhang, et al., 2019). Forkhead box 2 (FOXR2) is a tumor-promoting factor in cancer. FOXR2 upregulation significantly enhanced cancer metastasis via EMT induction (Lu, Qiu, et al., 2017). Silencing of FOXR2 suppressed lung cancer progression by reducing the expression of Wnt (Wang, Cui, et al., 2018). In ovarian cancer cells, circCELSR1 participated in PTX resistance by reducing the expression of miRNA-1252, and increasing the expression of FOXR2 (Zhang, Cheng, et al., 2020).

Most of the studies have focused on the role of tumor-promoting circRNAs in cancer cells exposed to PTX. The circ-ABCB10 is one such circRNA that increases cancer growth and viability via downregulation of miRNA-1271 (Liang, Zhang, et al., 2017). Overexpression of circ-ABCB10 was correlated with worse clinicopathological features and poor survival (Chen, Ye, et al., 2019). In breast cancer cells, upregulation of circ-ABCB10 increased PTX resistance. Circ-ABCB10 bound to the miRNA let-7a-5p to decrease its expression, leading to the accumulation of dual-specificity phosphatase 7 (DUSP7), inhibition of apoptosis, and PTX resistance (Yang, Gong, et al., 2020). PTX administration can affect cancer cell biology via modulation of circRNAs. PTX increased the

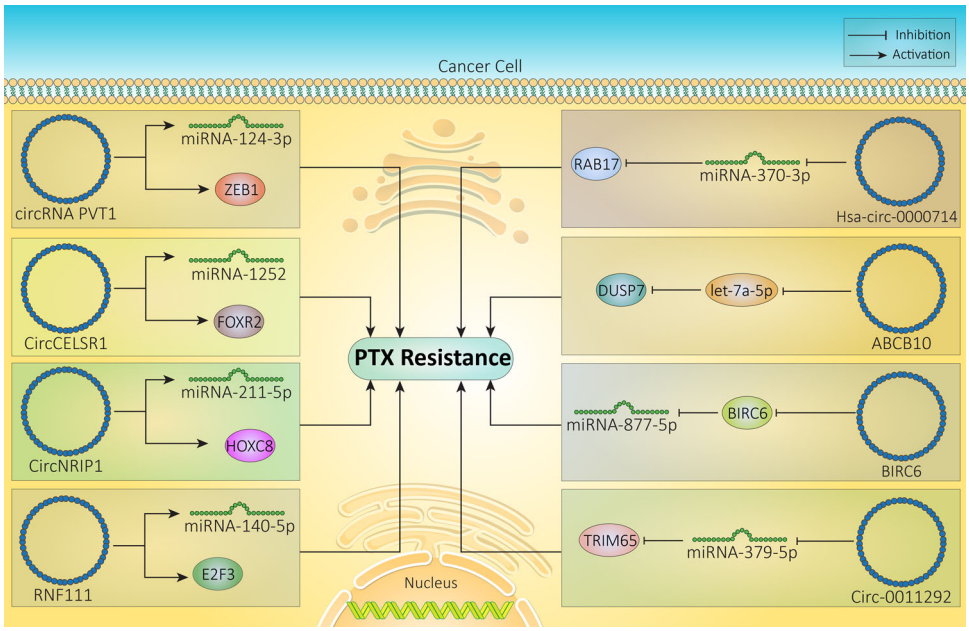

FIGURE 5 Similar to lncRNAs, circRNAs mainly target miRNAs in affecting response of cancer cells to PTX chemotherapy

expression of the tumor-suppressor miRNA-877-5p, resulting in YWHAZ downregulation and inhibition of hepatocellular carcinoma progression (Liu, Guo, et al., 2020). Hsa-circ-0028007 increased tumor growth and lymph node metastasis, and reduced the PTX sensitivity of nasopharyngeal carcinoma cells (Qiongna, Jiafeng, et al., 2020). Circ-cRNAs can regulate the expression of Akt as a tumor-promoting factor. CircAMOTL1 overexpression was associated with Akt upregulation and downregulation of pro-apoptotic factors including Bax and Bak, while the anti-apoptotic protein Bcl-2 was upregulated, leading to PTX resistance (Ma, Fang, et al., 2019).

The circRNA RNF111 can regulate the expression of miRNAs to affect cancer progression. In gastric cancer cells, RNF11 showed an inverse relationship with miRNA-27b-3p to increase proliferation, metastasis, and viability (Wang, Wang, et al., 2020). RNF111 diminished miRNA-140-5p expression to enhance E2F3 expression and increase PTX resistance in breast cancer cells. The RNF111 axis promoted invasion, proliferation, and glycolysis in breast cancer cells, leading to PTX resistance (Zang et al., 2020). Circ-0011292 has a similar effect to increase PTX resistance in small cell lung cancer cells, where it decreased miRNA-379-5p expression to increase the expression of tripartite motif-containing protein 65 (TRIM65) and promote PTX resistance. upregulated miRNA-379-5p expression was correlated with TRIM65 downregulation and reversing the tumor-promoting role of circ-0011292 (Guo, Wang, et al., 2020). It can be concluded that circRNAs mainly regulate the response of cancer cells to PTX chemotherapy by affecting miRNAs (Qiongna, Jiafeng, et al., 2020). Further studies can answer the question of whether there is any feedback loop between circRNAs and miRNAs in PTX chemotherapy, which is valuable in developing novel therapeutics in the near future.

Cyclin-dependent kinase 8 (CDK8) is a key member of the CDK family, which affects biological processes such as angiogenesis, stem cell self-renewal, etc. (Lim and Kaldis 2013). CDK8 enhances progression of cancer cells, and its pharmacological inhibition by anti-tumor compounds (such as capsaicin) reduces cancer malignancy (Spear, Lu, et al., 2020; Xia, Zhao, et al., 2020). Circ-0006528 upregulated CDK8 expression via inhibition of miRNA-1299 to promote PTX resistance in breast cancer cells (Liu, Zhang, et al., 2020). To date, only this one study has evaluated the regulation of CDK8 by circRNAs and the effect on PTX chemotherapy, suggesting that further studies are needed on circRNAs with regulatory effects on CDK8 (Figure 5 and Table 5).

9 | ncRNAs AS RELIABLE BIOMARKERS

Biomarker is a general term explaining various kinds of objective indicators of health or disease (Condrat, Thompson, et al., 2020). With respect to progress in the field of technology, these indicators have become more precise and reliable. Pulse, looks, and taste of urine were considered as biomarkers in ancient times. However, the biomarkers should be reliable in terms of providing diagnosis and prognosis. In the cancer field, the concept of biomarker is completely complicated and a biomarker should be reliable enough in predicting cancer development. Furthermore, the nature of biomarker is important, so that this biomarker should be obtained in a noninvasive or minimally invasive way. Therefore, scientists consider miRNAs as appropriate biomarkers, since their expression level undergoes deregulation in cancers, and they can also determine response of cancer cells to chemotherapy (Filipów & Łaczmański, 2019). These findings also apply to PTX. For instance, miRNA-30a-5p can be considered as a reliable biomarker for patients with lung cancer, since it has a tumor-suppressing role, and when its expression undergoes

TABLE 5 Circular RNAs and their role in paclitaxel chemotherapy

CircRNA	Cancer type	Effect on paclitaxel chemotherapy	Results	References
PVT1	Gastric cancer	Resistance	Downregulated miRNA-124-3p expression via sponging Increased ZEB1 expression Increased cancer malignancy and PTX resistance	Liu, Zhang, et al. (2019)
CircCELSR1	Ovarian cancer	Resistance	Sponging of miRNA-1252 Increased FOXR2 expression Induced PTX resistance	Zhang, Cheng, et al. (2020)
Hsa-circ-0000714	Ovarian cancer	Resistance	Induced RAB17 expression via miRNA-370-3p sponging Promoted proliferation and cell cycle progression	Guo, Wang, et al. (2020)
CircNRIP1	Ovarian cancer	Resistance	Decreased miRNA-211-5p via sponging Enhanced HOXC8 expression	Wu, Jia, et al. (2020)
Circ-0006528	Breast cancer	Resistance	Enhanced CDK8 expression via miRNA-1299 downregulation Triggered autophagy, proliferation, and metastasis Apoptosis inhibition	Wu, Zhong, et al. (2020)
RNF111	Breast cancer	Resistance	MiRNA-140-5p downregulation E2F3 overexpression Enhanced proliferation via glycolysis induction Promoted cancer metastasis	Zang, Li, et al. (2020)
ABCB10	Breast cancer	Resistance	Stimulated DUSP7 expression via let-7a-5p downregulation Enhanced tumor growth and apoptosis inhibition	Yang, Gong, et al. (2020)
BIRC6	Hepatocellular carcinoma	Resistance	Enhanced expression of miRNA-877-5p as a tumor-suppressing factor via BIRC6 inhibition Reduced cell viability and triggered apoptosis via YWHAZ inhibition	Liu, Guo, et al. (2020)
Hsa-circ-0028007	Nasopharyngeal carcinoma	Resistance	Overexpressed in cancer cells and tissues Mediated cancer metastasis and invasion Increased PTX resistance	Qiongna, Jiafeng, et al. (2020)
Circ-0011292	Non-small cell lung cancer	Resistance	InducedTRIM65 expression via miRNA-379-5p downregulation Increased carcinogenesis and PTX resistance	Guo, Wang, et al. (2020)

downregulation, it provides a poor response to PTX chemotherapy (Xu, Jin, et al., 2017). The same phenomenon occurs in cervical cancer. The miRNA-125a enhances PTX-mediated apoptosis in cervical cancer cells, and if its expression level is low, it predicts poor response to PTX chemotherapy (Fan, Cui, et al., 2016). Similarly, lncRNAs can be considered as biomarkers of response to PTX therapy, and their serum level is of importance (Huang, Wang, et al., 2019; Liu, Jiang, et al., 2020). It is worth mentioning that these

studies are related to pre-clinical, and the next step is translating these findings to clinic in predicting PTX response of cancer patients and adopting strategies for improving the efficacy of chemotherapy.

10 | CONCLUSION AND FUTURE OUTLOOK

In the present review, the role of the three main classes of ncRNAs in stimulating or inhibiting PTX resistance in cancer chemotherapy was mechanistically discussed. MiRNAs can be divided into two groups, including tumor-suppressor miRNAs and tumor-promoting miRNAs. Tumor-promoting miRNAs enhance the proliferation and migration of cancer cells and increase PTX resistance. Furthermore, this type of miRNAs stimulates cell cycle progression. These miRNAs were summarized in Table 2, and it can be seen that a wide variety of molecular pathways are involved as their downstream targets. Mad2, DAPK2, mTOR, STAT3, Akt, PTEN, and ERK are some of the downstream targets of miRNAs that can trigger PTX resistance. On the other hand, there are other tumor-suppressor miRNAs that affect the expression of different molecular pathways, such as E2F1, Bcl-2, Bad, Pak2, Wnt, and Akt. These miRNAs tend to trigger cancer cell apoptosis and suppress metastasis, resulting in increased PTX sensitivity. The piRNAs are another kind of short ncRNAs capable of regulating response of cancer cells to PTX chemotherapy. The important point is the role of siRNAs and shRNAs in reversing PTX resistance. It is possible to artificially siRNAs and shRNAs for targeting specific molecular pathways and enhancing PTX sensitivity of cancer cells.

The role of lncRNAs in PTX resistance or sensitivity was examined in depth. MiRNAs are the most well-known downstream targets of lncRNAs, which affect the response of cancer cells to PTX chemotherapy. By targeting miRNAs, lncRNAs can regulate the expression of molecular pathways, such as EMT, DOCK4, ABCB1, CDK6, and PBLD, which can then affect PTX resistance or sensitivity. Noteworthy, miRNAs affect the expression of target genes by binding to the 3′-UTR of the mRNA, while lncRNAs generally influence miRNA expression via sponging.

CircRNAs can also regulate the response of cancer cells to PTX therapy and similar to lncRNAs, they generally affect miRNAs. Their downstream targets include ZEB1, FOXR2, HOXC8, CDK8, and DUSP7, which can undergo upregulation or downregulation. These complex signaling networks can be taken into consideration to develop novel therapeutic approaches to improve PTX sensitivity.

Future combination therapy approaches could be investigated to devise routes to administer PTX at the same time as agents that can favorably modulate ncRNAs to improve sensitivity. If these agents are small molecules, then normal pharmacokinetic considerations for dual drug therapy will apply. However, if these agents are oligonucleotides, proteins, or other large molecules, it will likely be necessary to load both the agent and PTX into a nanovehicle that can be targeted to accumulate at the tumor site. Because PTX itself is a hydrophobic drug, it will also benefit from the use of a drug-delivery vehicle. Furthermore, clinical studies will be required to demonstrate the value of targeting ncRNAs to enhance the efficacy of PTX as a cancer chemotherapy drug.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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