Roles of circRNAs in cancer chemoresistance (Review)

CHUAN XIN*, FEI HUANG*, JIONGKE WANG, JING LI and QIANMING CHEN

State Key Laboratory of Oral Diseases, National Clinical Research Center for Oral Diseases, Chinese Academy of Medical Sciences Research Unit of Oral Carcinogenesis and Management, West China Hospital of Stomatology, Sichuan University, Chengdu, Sichuan 610041, P.R. China

Received October 18, 2020; Accepted March 11, 2021

DOI: 10.3892/or.2021.8176

Abstract. Circular RNA (circRNA) is a type of endogenous, high-stability, noncoding RNA. circRNAs exhibit various biological functions, and are involved in physiological and pathological processes occurring in various diseases, including cancers. They can not only act as microRNA and protein sponges, but also interact with proteins, translated peptides, and transcriptional and translational regulators, and compete with pre-mRNA splicing. Chemotherapy is one of the most important types of cancer treatment. However, the resistance of cancer cells to chemotherapy is a leading reason for the failure of chemotherapy. It has been reported that circRNAs play important roles in cancer resistance via a number of mechanisms. The functions of the circRNAs provide insight into their roles in chemoresistance pathways. In addition, some circRNAs may serve as novel biomarkers for the diagnosis and prognosis of cancer resistance. Obtaining improved understanding of the molecular regulatory networks featuring circRNAs in tumors and searching for markers for the diagnosis and treatment of cancer resistance are leading issues in circRNA research. The present review introduced the functions of circRNAs, illustrated the mechanisms underlying drug resistance in cancer, described the contributions of circRNAs to this resistance and discussed the potential application of circRNAs in the treatment of drug-resistant cancer. In particular, the review aimed to reveal the main mechanisms of circRNAs in cancer drug resistance, including mechanisms involving drug transport and metabolism, alterations of drug targets, DNA damage repair, downstream resistance mechanisms, adaptive responses and the tumor microenvironment. The findings may provide novel therapeutic targets for clinical treatment of cancer chemoresistance.

Correspondence to: Professor Jing Li or Dr Jiongke Wang, State Key Laboratory of Oral Diseases, National Clinical Research Center for Oral Diseases, Chinese Academy of Medical Sciences Research Unit of Oral Carcinogenesis and Management, West China Hospital of Stomatology, Sichuan University, 14 3rd Section of Ren Min Nan Road, Chengdu, Sichuan 610041, P.R. China
E-mail: lijing1984@scu.edu.cn
E-mail: wangjiongke@163.com

*Contributed equally

Key words: cancer drug resistance, cancer therapy, chemoresistance, circular RNA

Contents

1. Introduction

Circular RNAs (circRNAs/circs) are a type of noncoding RNA lacking 5'-3' ends and poly(A) tails, with a closed-loop structure that is more stable than that of linear RNA (1). circRNAs were first revealed to exist via electron microscopy in 1976 (2). In 1991, the first spliced circRNAs were discovered through analyses of a human candidate tumor suppressor gene (3). Despite extensive research, no evidence of the translation of circRNAs has been found, and researchers typically considered circRNAs to be the result of splicing errors (3). However, in early 2012, researchers were surprised to find that circRNA was a transcriptional product of thousands of human and mouse genes (4).

circRNAs can be roughly divided into three categories based on their genomic origin. Exonic circRNAs, the main type of circRNA, are formed via exon skipping or head-to-end connection. Intronic circRNAs are composed of lariat introns (5). Exon-intron circRNAs, which comprise the third category, consist of both exons and introns (5). Exonic circRNAs indicate the development of disease, and can be used as noninvasive biomarkers for diagnosis and prognosis in a number of diseases (6).

In the last few decades, the development of improved chemotherapy regimens with multiple chemotherapeutics, such as 5-fluorouracil (5-FU), and molecular targeting drugs, such as erlotinib and gemcitabine, have provided various treatments and significantly extended the survival time of patients

with cancer (7). However, the acquisition of resistance to chemotherapeutics is an intractable problem in clinical chemotherapy for cancer, reducing the effectiveness of treatment. To escape the attack of multiple chemotherapeutics, cancer cells have evolved multiple strategies, including promoting drug transport, altering drug targets, elevating DNA repair capacity, evading apoptosis and autophagy, and promoting adaptive responses (8). Nevertheless, the exact mechanisms of chemotherapy resistance remain to be fully elucidated.

With increasing in-depth research, circRNAs have been found to serve important roles in cancer development, including cancer proliferation, metastasis, chemoresistance and radioresistance, suggesting the potential of circRNA as a new tool for overcoming tumor resistance. The present study focused on the signaling pathways via which circRNAs promote the development of tumor chemoresistance, with the aim of finding general molecular mechanisms that stimulate further exploration of the pathway(s) through which circRNAs are involved in chemoresistance and therapeutic targets associated with these pathways.

2. Function of circRNAs

Multiple functions of circRNAs have been revealed; circRNAs can not only act as microRNA (miRNA/miR) sponges, protein sponges, and transcriptional and translational regulators, but also interact with proteins and translated peptides, and compete with pre-mRNA splicing (9). These functions may provide insight into the roles of circRNAs in the chemoresistance pathway.

miRNA sponges. Endogenous circRNAs can act as sponges of miRNAs and modulate the effects of miRNAs on target genes (10). miRNA dysregulation has been confirmed to play important roles in cancer growth via several mechanisms, including changes in genomic miRNA copy numbers and gene locations (11,12). The discovery of the circRNA-miRNA code has increased understanding of the dysregulation of miRNAs. For example, circ-DOCK1 can regulate baculoviral IAP repeat-containing protein 3 by sponging miR-196a-5p and thereby participating in the regulation of oral squamous cell carcinoma (OSCC) (13). However, the effects of circRNAs on their potential sponge miRNAs in chemoresistance remain largely undiscovered (14). Furthermore, concerns regarding the quantity of circRNAs required to achieve a measurable effect have been proposed due to the low levels of circRNAs and limited binding sites with miRNAs in cells (15).

Protein sponges and interactions with proteins. In addition to interacting with miRNA, circRNAs are processed cotranscriptionally to combine with various proteins as protein sponges or protein scaffolds (14). An example of circRNAs serving as protein scaffolds is the feedback loop between mannose-binding lectin (MBL) and circ-MBL (16). Excess levels of MBL promote the expression of circ-MBL, which absorbs the excess MBL, thereby decreasing its own mRNA expression and maintaining a balance in MBL production (14). Furthermore, circRNAs have been reported to engage with proteins and sequester proteins. For example, it was reported that the CDK2 and p21 can bind to circ-FoxO3 and form a circ-FoxO3-p21-CDK complex; the formation of this circ-FoxO3-p21-CDK2 complex can inhibit the function of CDK2 and induce cell cycle disorders (17). Furthermore, circ-FoxO3 can also interact with E2F1, ID-1, hypoxia-inducible factor 1α and focal adhesion kinase as an upstream signaling molecule (9). Thus, circRNAs can participate in and regulate a variety of cellular behaviors through proteins.

Transcriptional and translational regulators. To regulate gene transcription, the sequence of the circRNA itself is duplicated with the DNA sequence of the host gene. When circRNA stays in the nucleus for a certain period of time, it will form an RNA:DNA hybrid strand with the maternal DNA double strand. Under these circumstances, the maternal DNA transcription of other transcripts will be halted, which is referred to as negative feedback loop regulation (18). In addition, circRNAs have the potential to be pseudogenes; some circRNAs can be inserted into the genome to alter the genetic information of the genome via retrotransposition, regulating gene expression (19). A computational pipeline, CIRCpseudo, was developed to identify potential circRNA-derived pseudogenes in the mouse reference genome, and it was found that circ-SATB1 from mouse can be inserted into the CTCF gene sequence as a pseudogene (19).

Although circRNAs have been found to be predominantly located in the cytoplasm, circRNAs in the nucleus are involved in the regulation of transcription, alternative splicing and chromatin looping (20). circRNAs formed by processed intron lariats (ciRNAs) or by back-splicing with retained introns (EIciRNAs) are limited to the nucleus in human cells (14). RNA polymerase II (Pol II) consists of U1 small nuclear ribonucleoprotein (snRNP) and other proteins, and EIciRNA-U1 snRNP complexes can combine with RNA Pol II at the promoters of their parent genes to enhance gene expression (14). Additionally, a ciRNA called ci-ankrd52 was revealed to modulate RNA Pol II transcription by accumulating at its own sites of transcription (21).

Furthermore, circRNAs have been found to play an essential regulatory role in translation. circ-polyadenylate binding protein 1 (PABPN1) has been shown to sequester HuR to regulate the translation rate of the PABPN1 gene and reduce PABPN1 translation (22). The ribosome is the main organelle involved in translation; it was reported that the circ-ANRIL can modulate ribosomal RNA maturation to control ribosome biogenesis and nucleolar stress (23), which highlights the association between circRNA and translation regulation.

circRNAs can be translated. Most endogenous circRNAs cannot be translated, as they lack a 5' 7-methylguanosine triphosphate cap and a 3'-end poly(A) tail (20). However, studies have shown that certain endogenous circRNAs can be translated into proteins or peptides (24). The majority of circRNAs spliced from coding genes contain open reading frames (ORFs) and thus have protein coding potential (25). Although thousands of circRNAs are predicted to contain putative ORF and upstream internal ribosome entry sites (IRESs), to date only a few endogenous circRNAs, such as circ-PINTexon2, circ-F-box/WB repeat-containing protein 7, circ-Mb1, circ-zinc finger protein 609 (ZNF609) and circ-SHPRH, have been shown to be useful protein

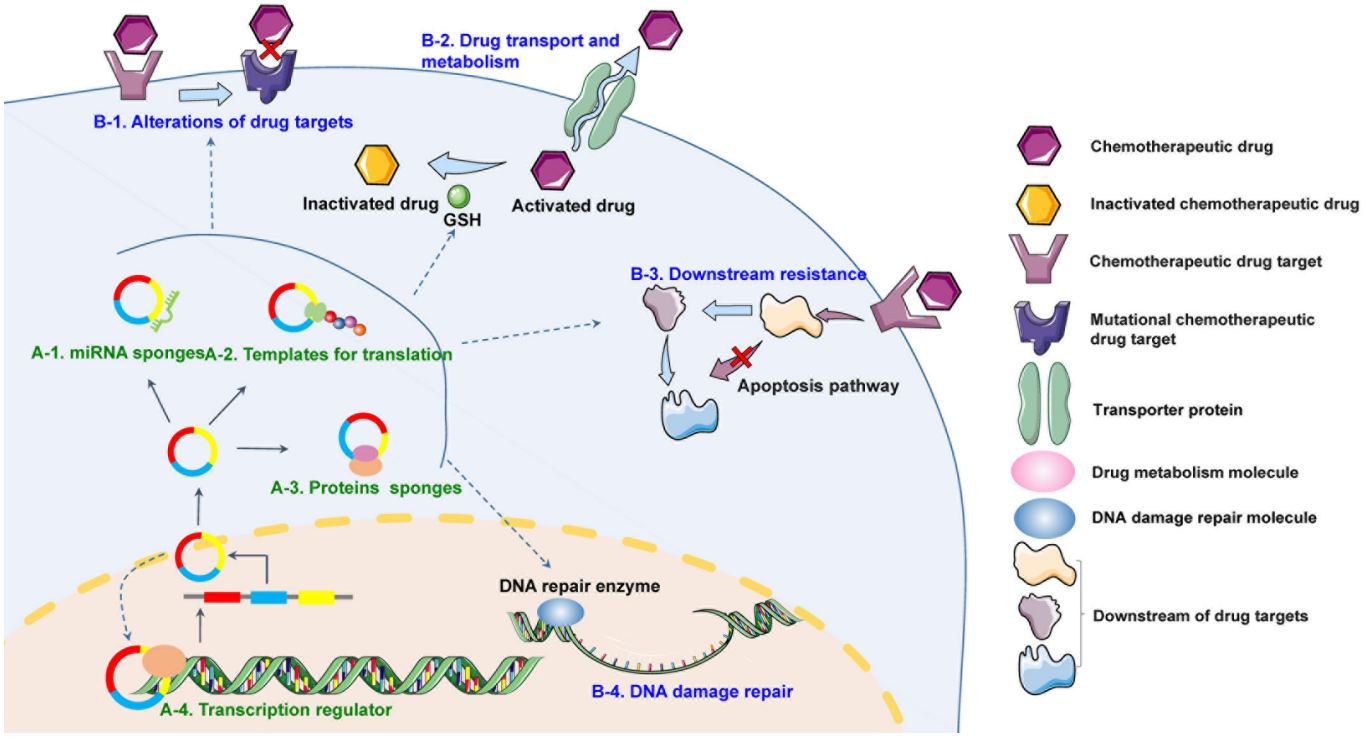

Figure 1. Mechanisms of circRNA involvement in chemotherapy resistance. Typical circRNAs are formed by precursor mRNA back-splicing or exon-skipping events in eukaryotes. (A) General mechanisms of circRNA functions in chemotherapy resistance. (1) circRNAs can sponge miRNAs, resulting in enhanced levels of ribosome binding and translation of target RNAs. (2) circRNAs with internal ribosome entry site elements and AUG sites may be translated and generate unique peptides. (3) Certain circRNAs can bind proteins to form circRNA-ribonucleoproteins, such as circ-FoxO3-p21-CDK, thus regulating their functions. (4) circRNAs can act as transcriptional regulators by recruiting specific proteins to certain loci or subcellular compartments. (B) Mechanisms via which circRNAs participate in chemotherapy resistance. (1) Alterations of drug targets. Drug inactivation resulting from alterations of drug targets is an important means of drug resistance. For example, increased expression of AR in prostate cancer has been found to reduce the efficacy of AR antagonists such as bicalutamide. (2) Drug transport and metabolism. Tumor cells can resist drug actions by promoting drug efflux via several cell membrane transporter proteins, such as members of the ATP-binding cassette transporter family, or drug inactivation; for instance, platinum drugs can be inactivated by the thiol GSH. (3) Downstream resistance. After drugs have inhibited their cellular target, various innate adaptive responses can be triggered to promote the survival of cancer cells, such as dysregulation of apoptosis pathways. (4) DNA damage repair. Tumor cells can avoid cell death and cell cycle arrest by promoting the repair of DNA damage induced by agents such as cisplatin. circRNA/circ, circular RNA; AR, androgen receptor; GSH, glutathione.

templates (26). Recently, it was found that ~50% of male germ cell circRNAs exhibited protein-coding potential, containing large ORFs and m6A-modified start codons in junction sequences (25). Additionally, a ~10 kDa protein encoded by circ-MBL3 has been detected via mass spectrometry (24). circ-ZNF609 contains an ORF and is translated into a protein in a splicing-dependent/cap-independent manner (26). Furthermore, circRNAs can promote the direct binding of translatable circRNAs to initiation factors or ribosomes, acting as IRESs (14). Furthermore, as circRNA-derived peptides are typically truncated forms of standard proteins lacking essential functional domains (26), they may serve as dominant-negative protein variants, decoys or modulators of alternative protein complexes.

3. Mechanisms of drug resistance in cancer

Chemotherapy is one of the main methods for treating malignancy, and multidrug resistance (MDR) is the main problem limiting the success of chemotherapy. The resistance of cancer cells can be categorized as primary resistance or acquired resistance. The former is resistance that existed in the tumor cells before the use of antitumor drugs, and is unassociated with their use. The latter is resistance induced by drug administration; that is, the cells were sensitive to the drug(s) before drug administration and became resistant afterwards. Acquired resistance may limit the application of chemotherapeutics and involves the gradual loss of the initial promising effect of chemotherapy. Numerous mechanisms have been described to explain MDR, including mechanisms involving drug transport and metabolism, alterations of drug targets, DNA damage repair, downstream resistance mechanisms, adaptive responses and the tumor microenvironment (Fig. 1) (8).

Drug transport and metabolism. Reducing the intracellular concentration of the drugs is an effective method for cancer cells to avoid the damage induced by drugs. A group of membrane proteins have been found to contribute to the drug resistance of commonly used antitumor drugs by promoting drug efflux. For example, multi-drug resistance (MDR)1, a member of the ATP-binding cassette (ABC) transporter family, has been reported to regulate the absorption, distribution and excretion of various anticancer drugs and inhibit the efficacy of chemotherapy in numerous cancers (27). Other ABC family transporters associated with MDR include multidrug resistance-associated protein 2 and breast cancer resistance protein (28). These three ABC transporters are commonly

co-expressed in cancer and exhibit a wide range of substrate specificity overlap involving drugs such as doxorubicin, epirubicin, etoposide, irinotecan and mitoxantrone (28). Drug metabolism is another important means to induce drug resistance, particularly when a chemotherapeutic drug is combined with a specific targeting molecule. For example, metallothionein and glutathione can bind cisplatin (CDDP), leading to drug inactivation (29).

Alterations to drug targets. Alterations to drug targets, such as mutations or changes in expression levels, may affect drug response and resistance. For example, altered expression of thymidylate synthase and ribonucleotide reductase reduces the effectiveness of inhibitors of these targets (30). Furthermore, cases of alterations to genes, including EGFR and anaplastic lymphoma kinase (ALK), leading to drug resistance have been observed. For example, a common drug resistance-related mutation, EGFR T790M, is associated with the acquisition of drug resistance (31). Additionally, in non-small cell lung cancer (NSCLC), gefitinib and erlotinib can activate mutations in the EGFR tyrosine kinase domain (32). In ALK-positive patients with NSCLC treated with tyrosine kinase inhibitor (TKI), ALK tyrosine kinase domain mutations or ALK fusion gene amplifications may occur (33).

DNA damage repair. A number of drugs, such as platinum and topoisomerase inhibitors, can lead to cell cycle arrest by inducing DNA damage, which will result in cancer cell death (34). However, some tumor cells can escape drug-induced damage by means of DNA damage repair, thus achieving drug resistance. The level of ERCC1-XPF has been found to be elevated in CDDP-treated testis tumor cells and result in increased DNA repair (35). It has been established that p53 is an important tumor suppressor protein for various types of human tumor; when platinum drugs cause damage to the DNA of tumor cells, p53 can initiate DNA damage repair and cell cycle arrest, and its mutation is frequently associated with drug resistance (36). To block the activation of DNA damage repair mechanisms, molecular targeting drugs have been developed, such as inhibitors of the single-strand-break DNA repair enzyme poly(ADP-ribose) polymerase 1; these drugs have proved effective against breast and ovarian tumors that involve mutations in the BRCA1 or BRCA2 genes (37). Therefore, targeting or blocking DNA repair processes is an effective treatment strategy.

Downstream resistance mechanisms. Even if enough active drug molecules accumulate on a cellular target, numerous intrinsic adaptive responses can be triggered that promote cancer cell survival (8). Under such conditions, cancer cells can evade drug-induced cell death in two ways: Apoptotic evasion and autophagy (8). Apoptosis is triggered when cells are in an adverse environment, such as the environment observed during anticancer therapy. Tumor cells have evolved multiple strategies to limit or evade apoptosis. One common way to block apoptosis is via the loss of the damage sensor TP53 (38). Autophagy is the process of phagocytosis and decomposition of cytoplasmic proteins or organelles by lysosomes; this process allows the resulting catabolites to be recycled to maintain cellular biosynthesis and viability (39). Paradoxically, nutritional starvation, radiation therapy and certain cytotoxic drugs can lead to elevated levels of autophagy, which instead of promoting the anticancer effects of chemotherapeutic drugs, has a protective effect on cancer cells (40). Numerous anticancer treatments can activate the autophagy pathway; conversely, hydroxychloroquine, an autophagy inhibitor, has been developed, and it can cause human cancer cells to become sensitive to chemotherapy (41).

Promotion of adaptive responses. The promotion of adaptive responses consists of three parts: Activation of prosurvival signaling, oncogenic bypass and pathway redundancy, and epithelial-mesenchymal transition (8). The addition of EGFR-targeted therapies to irinotecan-based chemotherapy in KRAS-wild-type colorectal cancer has shown beneficial effects. However, KRAS-mutant colorectal cancer is unresponsive to EGFR inhibitors as oncogenic KRAS is not dependent upon upstream activation by EGFR; this is an example of both activation of prosurvival signaling and oncogenic bypass resistance to EGFR inhibitors that was observed in cell lines undergoing epithelial-mesenchymal transition (42,43). EGFR-targeted drugs are promising for drug resistance treatment.

Tumor microenvironment. In both solid tumors and hematological malignancies, the complex tumor microenvironment provides shelter for cancer cells, protecting them from chemotherapeutic drugs and facilitating disease relapse. In addition, communication between cancer cells may mediate the development of chemoresistance (43). For example, increased expression of integrins can promote drug resistance (44). Furthermore, cytokines and growth factors are associated with resistance. Wilson *et al* (45) found that hepatocyte growth factor in the tissue microenvironment can induce drug resistance by reactivating either or both of the PI3K-AKT and MEK-ERK pathways. Moreover, exosomes play roles in the regulation of drug resistance. It has been shown that CDDP-resistant ovarian cancer cells release more protein and export higher levels of CDDP through exosomes than CDDP-sensitive cells (46). Exosomes containing miR-21 from CDDP-resistant OSCC cells were found to promote chemoresistance by targeting PTEN and programmed cell death protein 4 (PDCD4) in recipient OSCC cells (47).

Extrachromosomal circular DNA (ecDNAs). ecDNA, a type of circular DNA structure found outside of the normal chromosome structure, has begun to receive increasing attention. A previous study reported a novel targeted drug resistance mechanism mediated by ecDNA in glioblastoma: Tumor cells could show resistance to EGFR TKI by eliminating mutant EGFR in ecDNA (48). It is hypothesized that ecDNA is related to resistance mechanisms; however, there remains a lack of research in this area.

The mechanisms of drug resistance for different anticancer drugs during the process of drug resistance in different tumors do not exist independently. Multifaceted drug resistance pathways may complement each other during the development of drug resistance. An example is EGFR, which has been extensively studied; EGFR is involved in multiple mechanisms, including alterations of drug targets, dysregulation of apoptosis, activation of prosurvival signaling and epithelial-mesenchymal transition (8).

4. Mechanisms of circRNAs in cancer drug resistance

The mechanisms via which circRNAs promote drug resistance were divided into four categories: circRNA-miRNA patterns; fusion circRNAs; circRNA in exosomes; and mechanisms mediating chemoresistance potentially related to circRNAs in cancers. This classification emphasizes the roles of circRNAs in various drug-resistant pathways, providing a theoretical basis for future research aimed at overcoming tumor drug resistance with circRNAs as the targets.

circRNA-miRNA patterns. miRNAs serve important roles in cell development, cell differentiation, chemoresistance and the immune system, and function as oncogenes and tumor suppressors (49). For example, the FOXC1/miR-31-5p/large tumor suppressor kinase 2 pathway can modulate chemoresistance in colorectal cancer (50). Additionally, miR-375 can promote colorectal cancer cell sensitivity to 5-FU by directly targeting yes-associated protein 1 and SP1 (51). As sponges of miRNAs, circRNAs can modulate cancer cell chemoresistance by absorbing and degrading miRNAs (52). Identified circRNA-miRNA pathways involved in the development of cancer drug resistance are summarized in Table I. Most of the contributing studies aimed to elucidate the regulatory effects of circRNA-miRNA interactions on target proteins involved in chemoresistance. Several proteins listed in Table I, such as STAT3, EGFR and p53, are associated with the dysregulation of apoptosis, the activation of prosurvival signaling and DNA damage repair, respectively. Interactions between circRNAs and miRNAs can promote drug resistance by regulating protein expression (Fig. 2).

Research into circRNA-miRNA-protein three-stage regulatory networks has added an extra layer of complexity to understanding of cancer drug resistance; however, it also provides numerous potential targets to reverse chemoresistance that cover proteins and RNAs at same time. A recent study suggested that circRNA can promote gemcitabine resistance via autophagy regulation (53). Furthermore, numerous studies have found that circRNAs can influence tumor cell resistance to chemotherapy drugs via miRNA-mRNA axes (54-56). However, certain studies lack detailed resistance mechanisms; studies into the regulation of drug resistance via circRNA-protein pathways may neglect the involvement of miRNAs. The detailed mechanisms through which circRNAs are involved in tumor resistance remain unclear. At present, most research into modulation of cancer cell chemoresistance by circRNAs has focused on circRNA-miRNA pathways, which may overshadow circRNAs that regulates cancer drug resistance via other mechanisms.

Fusion circRNAs (f-circRNAs). As genes are misallocated due to abnormal chromosome translocations and chromosomal rearrangements, complementary repeating intron sequences such as the Alu-sequence may be introduced close enough to facilitate novel reverse splicing events during RNA maturation, leading to the production of abnormal circRNAs (57). Therefore, the juxtaposition of complementary sequences in the upstream and downstream introns of the translocation breakpoint region may form new circRNAs, called f-circRNAs, which are formed from the fusion of two translocation genes (57). Roles for this new type of circRNA in chemotherapy resistance have been identified. For example, in acute promyelocytic leukemia, general translocation occurs between the promyelocytic leukemia protein (PML) and retinoic acid receptor (RAR) genes, which then form f-circRNAs (58). F-circ-M9_1 and f-circ-M9_2 are two f-circRNAs formed via MLL/AF9 translocation in acute myeloid leukemia; it was reported that f-circM9 can promote chemotherapy resistance in acute myeloid leukemia (57). Furthermore, an f-circRNA from the BCR-ABL1 fusion gene, circ-BA9.3, was found to be associated with resistance to TKIs by increasing the production of C-ABL1 or BCR-ABL1 protein in leukemic cells (59).

circRNA in exosomes. Exosomes, containing a variety of proteins, DNA, mRNA, miRNA and other molecules, serve important roles in intercellular communication and the triggering of physiological responses (60). It has been reported that exosomes released from CDDP-resistant OSCC cells transmit miR-21, which targets PTEN and PDCD4 to decrease the drug resistance of OSCC cells (47). circ-CDR1as, which suppresses CDDP resistance in ovarian cancer, has been reported to be downregulated in serum exosomes from CDDP-resistant patients (61). However, the mechanism via which exosomes regulate drug resistance in ovarian cancer cells is unclear. Additionally, exosomal circ-Myc in the serum is associated with recurrence and bortezomib resistance in multiple myeloma (62). Recently, it was observed that exosomal circ-nuclear factor 1 X-type (NFIX) was upregulated in the serum of temozolomide (TMZ)-resistant patients and exosomal circ-NFIX from TMZ-resistant cells conferred TMZ resistance to recipient sensitive cells in glioma (63). This newly identified resistance mechanism may provide novel resistance targets.

Mechanisms mediating chemoresistance potentially related to circRNAs in cancers. circRNAs participate in the regulation of cancer cell chemoresistance not only by interacting with miRNAs, but also by affecting certain signaling pathways. Tumor resistance involves the mutual regulation of signaling networks. For example, BRCA1 serves an important role in the homology-directed repair of DNA double-strand breaks, which modulates chemotherapy resistance (64). AKT activation regulates resistance to CDDP-induced apoptosis by inhibiting apoptosis-inducing factor-related pathways (65). Furthermore, circ-PAN3 facilitates drug resistance in acute myeloid lymphoma cells via the AMPK/mTOR pathway (66). circ-mitochondrial tRNA translation optimization 1 reverses monastrol resistance by regulating the TNF receptor associated factor 4/Eg5 axis (67). In addition, circ-plasmacytoma variant translocation 1 facilitates the expression of ABCB1 to enhance the doxorubicin and CDDP resistance of osteosarcoma cells (67). It has been reported that lung adenocarcinoma can activate autophagy via the AMPK/mTOR signaling pathway and thus induce CDDP resistance (68). Additionally, ABCB1 is involved in drug transport and metabolism (69). However, there are few studies concerning the direct binding of circRNAs to proteins to regulate drug resistance.

circRNAs are involved in multiple drug resistance pathways and can form complex drug-resistance networks. The roles of circRNAs in resistance, including circRNA-miRNA interactions, circRNA-protein interactions and F-circRNAs, have been reviewed. However, some circRNAs have been

Table I. circRNAs-miRNAs and drug resistance.

First author, year	Cancer type	circRNA	Expression[a]	Validated/putative targets/pathways	Drug resistance-related effects	(Refs.)
Yan *et al*, 2019	Renal clear cell carcinoma	circ-0035483	Up	miR-335	Promotes gemcitabine resistance	(53)
Yang *et al*, 2019	Breast cancer	circ-CDR1as	Up	miR-7/CCNE1	Promotes docetaxel resistance	(79)
Huang *et al*, 2019	Gastric cancer	circ-AKT3	Up	miR-198/PIK3R1	Promotes CDDP resistance	(52)
Yu *et al*, 2019	Lung adenocarcinoma	circ-0003998	Up	miR-326	Promotes doxorubicin resistance	(80)
Shang *et al*, 2019	Acute myeloid leukemia	circ-PAN3	Up	miR-153-5p and miR-183-5p-XIAP	Promotes doxorubicin resistance	(81)
Kun-Peng *et al*, 2018	Osteosarcoma	circ-0004674	Up	miR-490-3p/ABCC2 and miR-1254/EGFR	Promotes doxorubicin/cisplatin/ methotrexate resistance	(82)
Liu *et al*, 2018	Thyroid cancer	circ-0060060	Up	miR-144-3p/TGF-α	Promotes CDDP resistance	(83)
Gao *et al*, 2019	Breast cancer	circ-000652	Up	miR-7-5p/Raf1	Promotes adriamycin resistance	(84)
Zhou *et al*, 2019	NSCLC	circ-0004015	Up	miR-1183/PDPK1	Promotes gefitinib resistance	(85)
Xu *et al*, 2018	NSCLC	circ-0000567	Up	miR-141	Promotes taxol resistance	(5)
Xu *et al*, 2018	NSCLC	circ-0091931	Down	miR-34c-5p/p53	Promotes taxol resistance	(5)
Hua *et al*, 2019	NSCLC	circ-0000567	Up	miR-124	Promotes pemetrexed resistance	(86)
Xiong *et al*, 2017	Colorectal cancer	circ-0000504	Up	miR-485-5p on STAT3	Promotes 5-FU resistance	(87)
Xiong *et al*, 2017	Colorectal cancer	circ-0007031	Up	miR-885-3p/AKT3/BCL2	Promotes 5-FU resistance	(87)
Xiong *et al*, 2017	Colorectal cancer	circ-0048234	Down	miR-671-5p/EGFR	Promotes 5-FU resistance	(87)
Sang *et al*, 2019	Breast cancer	circ-0025202	Down	miR-182-5p/FoxO3a	Suppresses tamoxifen resistance	(76)
Zhu *et al*, 2019	Osteosarcoma	circ-0001258	Down	miR-744-3p/GSTM2	Suppresses drug resistance	(88)
Chi *et al*, 2019	Bladder cancer	circ-0000285	Down	miR-124 or miR-558	Suppresses CDDP resistance	(89)
Wu *et al*, 2019	Prostate cancer	circ-0001427	Down	miR-181c-5p/ARv7	Suppresses enzalutamide resistance	(90)

[a]Expression in chemoresistant tumor tissue compared with non-tumor tissue. circRNA/circ, circular RNA; miRNA/miR, microRNA; 5-FU, 5-fluorouracil; CDDP, cisplatin; NSCLC, non-small cell lung cancer.

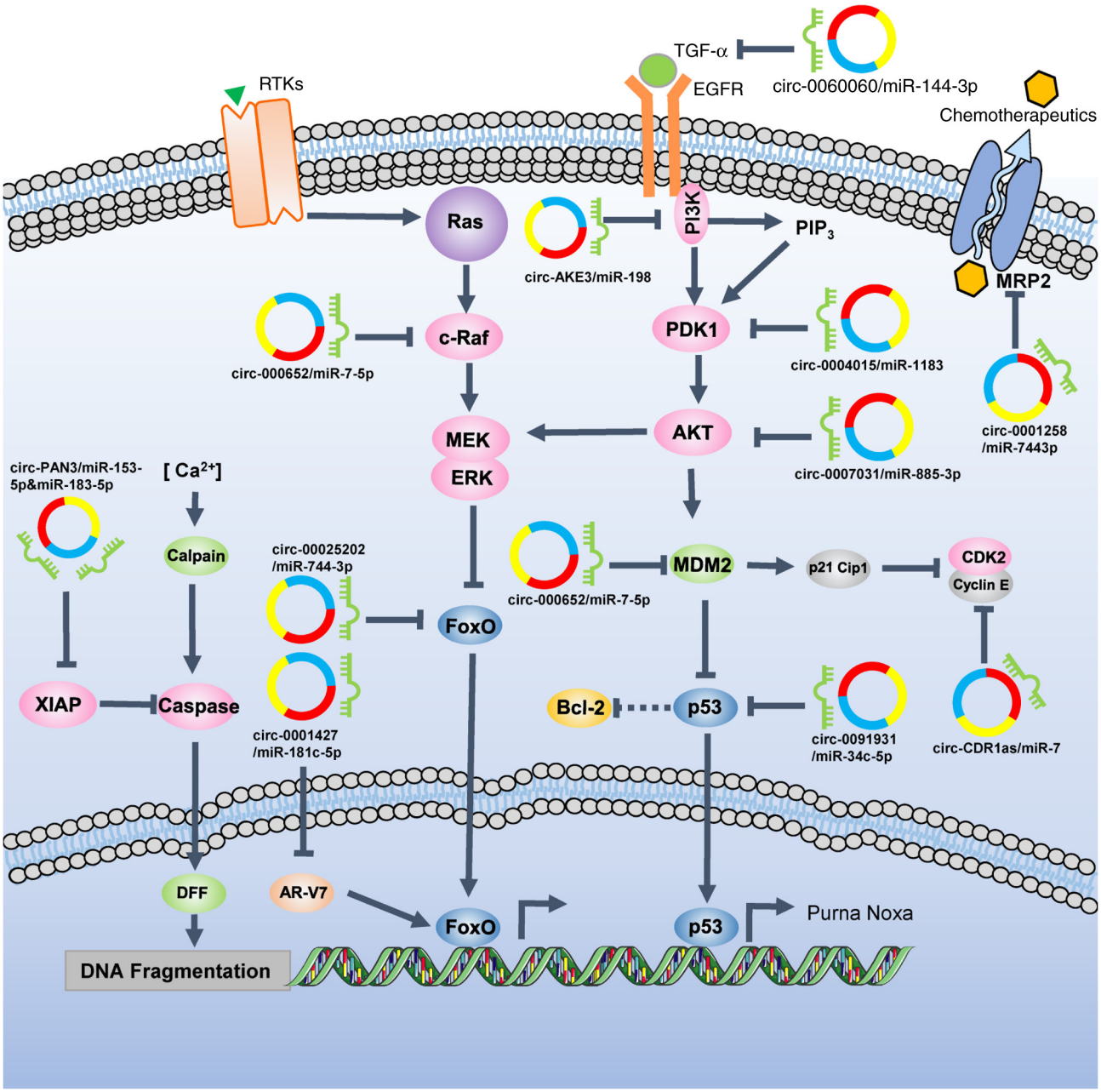

Figure 2. Network regulation of chemotherapy resistance via circRNA-miRNA interactions. In the apoptosis pathway, circ-PAN3 elevate the expression of XIAP by sponging miR-153-5p and miR-183-5p, thereby promoting DNA damage repair. circ-0001427 sponges miR-181c-5p, which targets AR-V7 and increases its expression, resulting in the reduced efficacy of AR antagonists. In the AKT-ERK regulatory network, circ-000652/miR-7-5p/c-Raf, circ-00025202/miR-744-3p/FoxO, circ-0060060/miR-144-3p/IGF, circ-0004015/miR-1183/PDK1, circ-0007031/miR-885-3p/AKT, circ-000652/miR-7-5p/MDM2, circ-0091931/miR-34c-5p/p53 and circ-CDR1as/miR-7/CDK2-cyclin E axes may induce proliferation signal transmission, leading to evasion of drug-induced cell death. By sponging miR-744-3p, circ-0001258 could increase the levels of MRP2, which can transfer chemotherapeutics out of cancer cells. circRNA/circ, circular RNA; miRNA/miR, microRNA; AR-V7, androgen receptor V7; DFF, DNA fragmentation factor; MDM2, mouse double minute homolog 2; MRP2, multidrug resistance-associated protein 2; PDK1, phosphoinositide-dependent protein kinase 1; RTK, receptor tyrosine kinase; XIAP, X-linked inhibitor of apoptosis protein.

identified to be associated with cancer drug resistance, but information concerning their mechanisms is lacking. For example, circ-0004350 and circ-0092857 are involved in the drug sensitivity of lung cancer, and circ-elongator complex protein 3 contributes to CDDP resistance (70,71). Additionally, circ-100053 can promote imatinib resistance in chronic myeloid leukemia (72), and circ-coiled-coil domain containing 66 can increase the EGFR resistance of lung adenocarcinoma cells (73). Nevertheless, the mechanisms via which these circRNAs alter drug resistance remain unclear. This topic merits further investigation, and future research may lead to the identification of potential protein targets to overcome chemotherapy resistance.

5. Potential applications of circRNAs in cancer drug resistance treatment

With developments in molecular oncology, targeted drugs that regulate drug resistance genes have become an important tool for reversing drug resistance. A previous study found

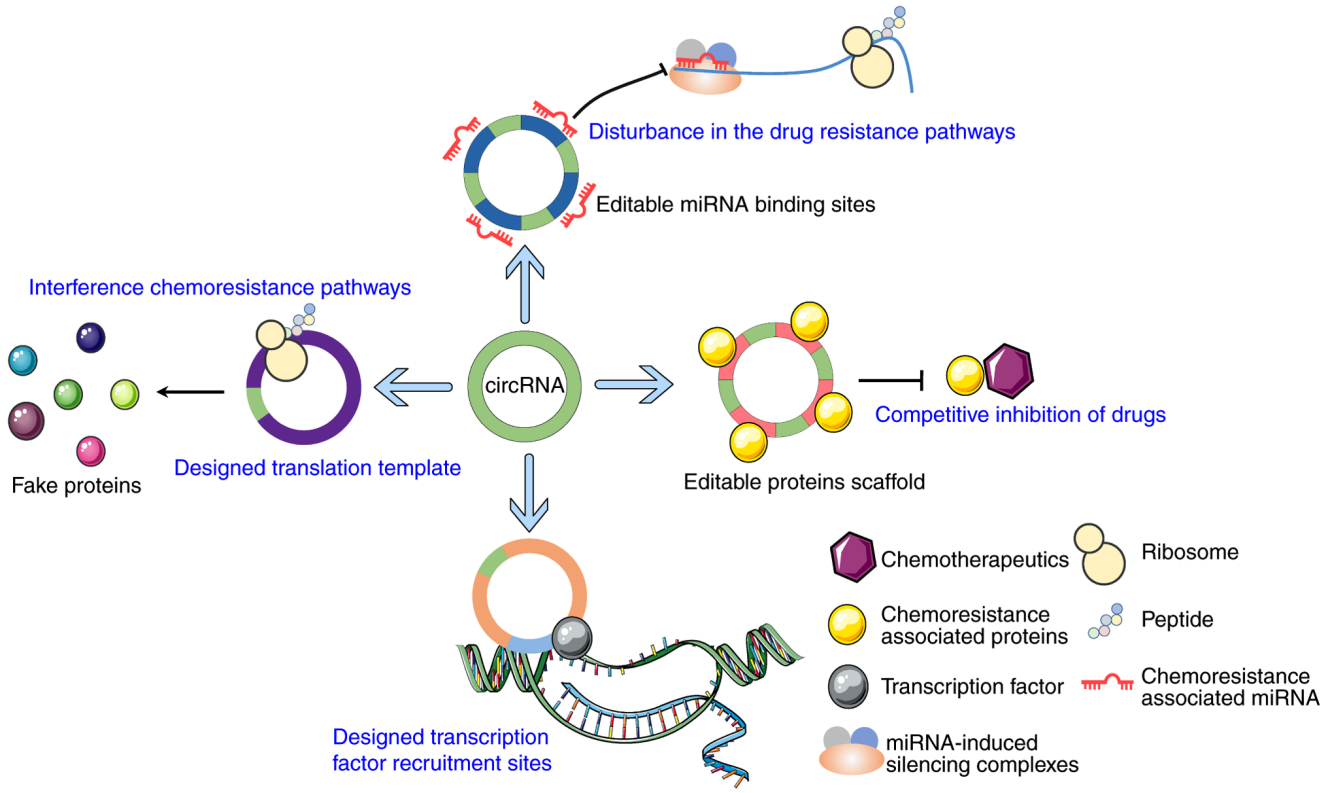

Figure 3. Potential applications of circRNAs in cancer drug resistance treatment. Targeted chemoresistance-associated miRNA binding sites can be designed into circRNAs to enable miRNA sponging, resulting in disturbance in drug resistance pathways. Based on specific protein-binding elements, circRNA can be used as a trap to sponge target chemoresistance-associated proteins, leading improved efficacy of drugs. circRNAs with internal ribosome entry site elements and AUG sites that are translated to generate unique peptides could be used as fake proteins that form small molecular weight translation templates to interfere with chemoresistance. In addition, circRNAs could be designed to recruit specific transcription factors to certain loci or subcellular compartments, resulting in regulation of targeted chemoresistance-associated genes. circRNA, circular RNA; miRNA, microRNA.

that RNA interference can significantly reduce the expression of STAT3, allowing the resensitization of resistant cancer cells (74). Findings concerning the multiple mechanisms of circRNA in cancer drug resistance have indicated the potential of circRNAs to serve as a new treatment tool.

One important mechanism of tumor resistance entails modulation of the regulatory effects of miRNA. *In vitro* research has suggested that certain miRNA mimics or antagomirs can enhance the treatment effect of anticancer drugs by regulating target protein expression (75). In the case of imbalanced circRNAs in drug-resistant cancer, circRNA levels could be adjusted by cloning the circRNA sequence and its regulatory flanking regions or by using small interfering RNA (siRNA). In various animal experiments, it has been shown that circRNA can be used as a target to achieve substantial therapeutic efficacy (52,76). Additionally, it has been reported that packaging siRNA in extracellular vesicles via a pre-microRNA backbone can allow a reduced therapeutic dose of siRNA (77). It is hypothesized that circRNA may serve as a novel type of miRNA vector with multiple miRNA adsorption target sites that promote chemoresistance in order to block drug resistance, utilizing the function of circRNA as a miRNA sponge.

It is proposed that circRNAs could be designed to sponge miRNAs and proteins that promote chemoresistance; due to the size of circRNAs, multiple sponge sites could be designed and incorporated to enhance their function. Additionally, as circRNAs can function as transcriptional and translational regulators, it may be possible to design artificial circRNAs to regulate the transcription and translation of essential genes involved in the pathway of drug resistance by interacting with their promoters. However, a lack of information concerning the mechanisms via which circRNA can act as a transcriptional and translational regulator is an obstacle to realizing this possibility. It may also be possible to design certain circRNAs similar to plasmids that can carry a target gene sequence and transmit it into cancer cells to express specific proteins and inhibit drug resistance (Fig. 3). Furthermore, it may be possible to design circRNAs with several of the functions mentioned above to enhance their ability to regulate drug resistance.

circRNAs are increasingly recognized as important factors in maintaining cellular homeostasis. circRNAs are closely associated with chemoresistance and may be used as potential therapeutic targets and prognostic markers in solid tumors or hematological malignancies. Furthermore, circRNAs may be used as an early marker of tumor drug resistance, as they can readily enter the circulatory system by the exosome pathway (52,63,78).

6. Conclusions and perspectives

The present review provided a novel perspective on the roles of circRNAs in chemotherapy resistance. By consulting studies into the various resistance pathways, it was found that most

research concerning the modulation of chemoresistance in cancer cells by circRNAs has focused on circRNA-miRNA pathways. Furthermore, a novel form of circRNA that has been discovered, f-circRNA, may play important roles in chemoresistance. circRNA research will increase present understanding of the mechanisms underlying tumor resistance and identify therapeutic targets to combat drug resistance. The detailed mechanisms via which circRNAs affect drug resistance remain to be elucidated.

Although not all drug resistance-associated circRNAs are included in this review, the studies summarized above demonstrate that circRNAs serve important regulatory roles in chemotherapy. circRNAs are involved in multiple drug resistance pathways and can form complex drug resistance networks. The roles of circRNA in resistance were reviewed, addressing circRNA-miRNA and circRNA-protein interactions, as well as f-circRNAs. However, some circRNAs have been identified to be associated with cancer drug resistance, but information on the mechanisms is lacking. Therefore, an in-depth understanding of the molecular mechanisms via which circRNAs participate in cancer resistance is required.

There is great promise concerning circRNAs that could serve as important biomarkers for diagnosis and prognosis in clinical settings. For example, Kaplan-Meier survival analysis revealed that recurrent patients with glioma in a low circ-NFIX expression group exhibited improved survival compared with those in the high circ-NFIX expression group (63). Additionally, a previous study reported that low levels of circ-AKT3 in patients with gastric cancer receiving CDDP therapy were associated with poorer 5-year disease-free survival (52). Furthermore, decreased expression of circ-KDM4C in breast cancer was associated with poorer overall survival (78). Accumulating evidence indicates that circRNAs may serve an important role in the diagnosis and prognosis of various tumors.

miRNAs and proteins that may be associated with drug resistance should be investigated for their relationships with circRNAs. There is great clinical potential for findings from research into circRNAs; however, due to the low intracellular concentrations of circRNAs, their adsorption and biological functions are limited. Additionally, the large number of resistance-related circRNAs may lead to failure in the treatment of drug resistance. Nevertheless, circRNAs exhibit great potential for overcoming drug resistance, especially for tumors that can readily develop chemoresistance.

Acknowledgements

Not applicable.

Funding

This work was supported by the National Natural Science Foundation of China (grant nos. 81872211, 81672675 and 81771081), the 111 Project of MOE China (grant no. B14038), the Sichuan University Innovation and Entrepreneurship Training Program for Undergraduates (grant no. C2019106455) and the Graduate Student's Research and Innovation Fund of Sichuan University (grant no. 2018YJSY018).

Availability of data and materials

Not applicable.

Authors' contributions

CX, FH, JL and JKW wrote the manuscript and designed the figures. JL and JKW provided guidance and revised the manuscript. QC revised this manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Bach DH, Lee SK and Sood AK: Circular RNAs in cancer. Mol Ther Nucleic Acids 16: 118-129, 2019.
2. Sanger HL, Klotz G, Riesner D, Gross HJ and Kleinschmidt AK: Viroids are single-stranded covalently closed circular RNA molecules existing as highly base-paired rod-like structures. Proc Natl Acad Sci USA 73: 3852-3856, 1976.
3. Nigro JM, Cho KR, Fearon ER, Kern SE, Ruppert JM, Oliner JD, Kinzler KW and Vogelstein B: Scrambled exons. Cell 64: 607-613, 1991.
4. Barrett SP and Salzman J: Circular RNAs: Analysis, expression and potential functions. Development 143: 1838-1847, 2016.
5. Xu N, Chen S, Liu Y, Li W, Liu Z, Bian X, Ling C and Jiang M: Profiles and bioinformatics analysis of differentially expressed circrnas in taxol-resistant non-small cell lung cancer cells. Cell Physiol Biochem 48: 2046-2060, 2018.
6. Zhou R, Chen KK, Zhang J, Xiao B, Huang Z, Ju C, Sun J, Zhang F, Lv XB and Huang G: The decade of exosomal long RNA species: An emerging cancer antagonist. Mol Cancer 17: 75, 2018.
7. Solassol I, Pinguet F and Quantin X: FDA- and EMA-Approved tyrosine kinase inhibitors in advanced EGFR-Mutated non-small cell lung cancer: Safety, tolerability, plasma concentration monitoring, and management. Biomolecules 9: 668, 2019.
8. Holohan C, Van Schaeybroeck S, Longley DB and Johnston PG: Cancer drug resistance: An evolving paradigm. Nat Rev Cancer 13: 714-726, 2013.
9. Lei K, Bai H, Wei Z, Xie C, Wang J, Li J and Chen Q: The mechanism and function of circular RNAs in human diseases. Exp Cell Res 368: 147-158, 2018.
10. Xiong DD, Dang YW, Lin P, Wen DY, He RQ, Luo DZ, Feng ZB and Chen G: A circRNA-miRNA-mRNA network identification for exploring underlying pathogenesis and therapy strategy of hepatocellular carcinoma. J Transl Med 16: 220, 2018.
11. Bayani J, Kuzmanov U, Saraon P, Fung WA, Soosaipillai A, Squire JA and Diamandis EP: Copy number and expression alterations of miRNAs in the ovarian cancer cell line OVCAR-3: Impact on kallikrein 6 protein expression. Clin Chem 59: 296-305, 2013.
12. Calin GA and Croce CM: MicroRNA signatures in human cancers. Nat Rev Cancer 6: 857-866, 2006.
13. Wang L, Wei Y, Yan Y, Wang H, Yang J, Zheng Z, Zha J, Bo P, Tang Y, Guo X, *et al*: CircDOCK1 suppresses cell apoptosis via inhibition of miR196a5p by targeting BIRC3 in OSCC. Oncol Rep 39: 951-966, 2018.
14. Li X, Yang L and Chen LL: The biogenesis, functions, and challenges of circular RNAs. Mol Cell 71: 428-442, 2018.

15. Guo JU, Agarwal V, Guo H and Bartel DP: Expanded identification and characterization of mammalian circular RNAs. Genome Biol 15: 409, 2014.
16. Kristensen LS, Hansen TB, Venø MT and Kjems J: Circular RNAs in cancer: Opportunities and challenges in the field. Oncogene 37: 555-565, 2018.
17. Du WW, Yang W, Liu E, Yang Z, Dhaliwal P and Yang BB: Foxo3 circular RNA retards cell cycle progression via forming ternary complexes with p21 and CDK2. Nucleic Acids Res 44: 2846-2858, 2016.
18. Conn VM, Hugouvieux V, Nayak A, Conos SA, Capovilla G, Cildir G, Jourdain A, Tergaonkar V, Schmid M, Zubieta C and Conn SJ: A circRNA from SEPALLATA3 regulates splicing of its cognate mRNA through R-loop formation. Nat Plants 3: 17053, 2017.
19. Dong R, Zhang XO, Zhang Y, Ma XK, Chen LL and Yang L: CircRNA-derived pseudogenes. Cell Res 26: 747-750, 2016.
20. Jeck WR, Sorrentino JA, Wang K, Slevin MK, Burd CE, Liu J, Marzluff WF and Sharpless NE: Circular RNAs are abundant, conserved, and associated with ALU repeats. RNA 19: 141-157, 2013.
21. Zhang Y, Zhang XO, Chen T, Xiang JF, Yin QF, Xing YH, Zhu S, Yang L and Chen LL: Circular intronic long noncoding RNAs. Mol Cell 51: 792-806, 2013.
22. Abdelmohsen K, Panda AC, Munk R, Grammatikakis I, Dudekula DB, De S, Kim J, Noh JH, Kim KM, Martindale JL and Gorospe M: Identification of HuR target circular RNAs uncovers suppression of PABPN1 translation by CircPABPN1. RNA Biol 14: 361-369, 2017.
23. Holdt LM, Stahringer A, Sass K, Pichler G, Kulak NA, Wilfert W, Kohlmaier A, Herbst A, Northoff BH, Nicolaou A, *et al*: Circular non-coding RNA ANRIL modulates ribosomal RNA maturation and atherosclerosis in humans. Nat Commun 7: 12429, 2016.
24. Pamudurti NR, Bartok O, Jens M, Ashwal-Fluss R, Stottmeister C, Ruhe L, Hanan M, Wyler E, Perez-Hernandez D, Ramberger E, *et al*: Translation of CircRNAs. Mol Cell 66: 9-21.e7, 2017.
25. Tang C, Xie Y, Yu T, Liu N, Wang Z, Woolsey RJ, Tang Y, Zhang X, Qin W, Zhang Y, *et al*: m^6A-dependent biogenesis of circular RNAs in male germ cells. Cell Res 30: 211-228, 2020.
26. Legnini I, Di Timoteo G, Rossi F, Morlando M, Briganti F, Sthandier O, Fatica A, Santini T, Andronache A, Wade M, *et al*: Circ-ZNF609 Is a Circular RNA that can be translated and functions in myogenesis. Mol Cell 66: 22-37.e9, 2017.
27. Thomas H and Coley HM: Overcoming multidrug resistance in cancer: An update on the clinical strategy of inhibiting p-glycoprotein. Cancer Control 10: 159-165, 2003.
28. Shapira A, Livney YD, Broxterman HJ and Assaraf YG: Nanomedicine for targeted cancer therapy: Towards the overcoming of drug resistance. Drug Resist Updat 14: 150-163, 2011.
29. Ghosh S: Cisplatin: The first metal based anticancer drug. Bioorg Chem 88: 102925, 2019.
30. Longley DB, Harkin DP and Johnston PG: 5-fluorouracil: Mechanisms of action and clinical strategies. Nat Rev Cancer 3: 330-338, 2003.
31. Hashida S, Soh J, Toyooka S, Furukawa M, Shien K, Yamamoto H, Asano H, Tsukuda K, Hagiwara K and Miyoshi S: Presence of the minor EGFR T790M mutation is associated with drug-sensitive EGFR mutations in lung adenocarcinoma patients. Oncol Rep 32: 145-152, 2014.
32. Sequist LV, Martins RG, Spigel D, Grunberg SM, Spira A, Jänne PA, Joshi VA, McCollum D, Evans TL, Muzikansky A, *et al*: First-line gefitinib in patients with advanced non-small-cell lung cancer harboring somatic EGFR mutations. J Clin Oncol 26: 2442-2449, 2008.
33. Shaw AT, Yeap BY, Solomon BJ, Riely GJ, Gainor J, Engelman JA, Shapiro GI, Costa DB, Ou SH, Butaney M, *et al*: Effect of crizotinib on overall survival in patients with advanced non-small-cell lung cancer harbouring ALK gene rearrangement: A retrospective analysis. Lancet Oncol 12: 1004-1012, 2011.
34. Zakharenko A, Dyrkheeva N and Lavrik O: Dual DNA topoisomerase 1 and tyrosyl-DNA phosphodiesterase 1 inhibition for improved anticancer activity. Med Res Rev 39: 1427-1441, 2019.
35. Usanova S, Piée-Staffa A, Sied U, Thomale J, Schneider A, Kaina B and Köberle B: Cisplatin sensitivity of testis tumour cells is due to deficiency in interstrand-crosslink repair and low ERCC1-XPF expression. Mol Cancer 9: 248, 2010.
36. Fan S, el-Deiry WS, Bae I, Freeman J, Jondle D, Bhatia K, Fornace AJ Jr, Magrath I, Kohn KW and O'Connor PM: p53 gene mutations are associated with decreased sensitivity of human lymphoma cells to DNA damaging agents. Cancer Res 54: 5824-5830, 1994.
37. Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, Santarosa M, Dillon KJ, Hickson I, Knights C, *et al*: Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 434: 917-921, 2005.
38. Hanahan D and Weinberg RA: Hallmarks of cancer: The next generation. Cell 144: 646-674, 2011.
39. White E, Mehnert JM and Chan CS: Autophagy, metabolism, and cancer. Clin Cancer Res 21: 5037-5046, 2015.
40. White E and DiPaola RS: The double-edged sword of autophagy modulation in cancer. Clin Cancer Res 15: 5308-5316, 2009.
41. Sasaki K, Tsuno NH, Sunami E, Tsurita G, Kawai K, Okaji Y, Nishikawa T, Shuno Y, Hongo K, Hiyoshi M, *et al*: Chloroquine potentiates the anti-cancer effect of 5-fluorouracil on colon cancer cells. BMC Cancer 10: 370, 2010.
42. Arnold D, Lueza B, Douillard JY, Peeters M, Lenz HJ, Venook A, Heinemann V, Van Cutsem E, Pignon JP, Tabernero J, *et al*: Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. Ann Oncol 28: 1713-1729, 2017.
43. Fuchs BC, Fujii T, Dorfman JD, Goodwin JM, Zhu AX, Lanuti M and Tanabe KK: Epithelial-to-mesenchymal transition and integrin-linked kinase mediate sensitivity to epidermal growth factor receptor inhibition in human hepatoma cells. Cancer Res 68: 2391-2399, 2008.
44. Hoyt K, Castaneda B, Zhang M, Nigwekar P, di Sant'agnese PA, Joseph JV, Strang J, Rubens DJ and Parker KJ: Tissue elasticity properties as biomarkers for prostate cancer. Cancer Biomark 4: 213-225, 2008.
45. Wilson TR, Fridlyand J, Yan Y, Penuel E, Burton L, Chan E, Peng J, Lin E, Wang Y, Sosman J, *et al*: Widespread potential for growth-factor-driven resistance to anticancer kinase inhibitors. Nature 487: 505-509, 2012.
46. Safaei R, Larson BJ, Cheng TC, Gibson MA, Otani S, Naerdemann W and Howell SB: Abnormal lysosomal trafficking and enhanced exosomal export of cisplatin in drug-resistant human ovarian carcinoma cells. Mol Cancer Ther 4: 1595-1604, 2005.
47. Liu T, Chen G, Sun D, Lei M, Li Y, Zhou C, Li X, Xue W, Wang H, Liu C and Xu J: Exosomes containing miR-21 transfer the characteristic of cisplatin resistance by targeting PTEN and PDCD4 in oral squamous cell carcinoma. Acta Biochim Biophys Sin (Shanghai) 49: 808-816, 2017.
48. Nathanson DA, Gini B, Mottahedeh J, Visnyei K, Koga T, Gomez G, Eskin A, Hwang K, Wang J, Masui K, *et al*: Targeted therapy resistance mediated by dynamic regulation of extrachromosomal mutant EGFR DNA. Science 343: 72-76, 2014.
49. Mohr AM and Mott JL: Overview of microRNA biology. Semin Liver Dis 35: 3-11, 2015.
50. Hsu HH, Kuo WW, Shih HN, Cheng SF, Yang CK, Chen MC, Tu CC, Viswanadha VP, Liao PH and Huang CY: FOXC1 regulation of miR-31-5p confers oxaliplatin resistance by targeting LATS2 in colorectal cancer. Cancers (Basel) 11: 1576, 2019.
51. Xu X, Chen X, Xu M, Liu X, Pan B, Qin J, Xu T, Zeng K, Pan Y, He B, *et al*: miR-375-3p suppresses tumorigenesis and partially reverses chemoresistance by targeting YAP1 and SP1 in colorectal cancer cells. Aging (Albany NY) 11: 7357-7385, 2019.
52. Huang X, Li Z, Zhang Q, Wang W, Li B, Wang L, Xu Z, Zeng A, Zhang X, Zhang X, *et al*: Circular RNA AKT3 upregulates PIK3R1 to enhance cisplatin resistance in gastric cancer via miR-198 suppression. Mol Cancer 18: 71, 2019.
53. Yan L, Liu G, Cao H, Zhang H and Shao F: Hsa_circ_0035483 sponges hsa-miR-335 to promote the gemcitabine-resistance of human renal cancer cells by autophagy regulation. Biochem Biophys Res Commun 519: 172-178, 2019.
54. Lapa RML, Barros-Filho MC, Marchi FA, Domingues MAC, de Carvalho GB, Drigo SA, Kowalski LP and Rogatto SR: Integrated miRNA and mRNA expression analysis uncovers drug targets in laryngeal squamous cell carcinoma patients. Oral Oncol 93: 76-84, 2019.
55. Chen D, Bao C, Zhao F, Yu H, Zhong G, Xu L and Yan S: Exploring specific miRNA-mRNA axes with relationship to taxanes-resistance in breast cancer. Front Oncol 10: 1397, 2020.
56. Kong F, He S, Shen X, Li L, Fang J and Lian M: Integrated analysis of different mRNA and miRNA profiles in human hypopharyngeal squamous cell carcinoma sensitive and resistant to chemotherapy. Neoplasma 67: 473-483, 2020.
57. Guarnerio J, Bezzi M, Jeong JC, Paffenholz SV, Berry K, Naldini MM, Lo-Coco F, Tay Y, Beck AH and Pandolfi PP: Oncogenic role of Fusion-circRNAs Derived from cancer-associated chromosomal translocations. Cell 165: 289-302, 2016.

58. Dos Santos GA, Kats L and Pandolfi PP: Synergy against PML-RARa: Targeting transcription, proteolysis, differentiation, and self-renewal in acute promyelocytic leukemia. J Exp Med 210: 2793-2802, 2013.
59. Pan Y, Lou J, Wang H, An N, Chen H, Zhang Q and Du X: CircBA9.3 supports the survival of leukaemic cells by up-regulating c-ABL1 or BCR-ABL1 protein levels. Blood Cells Mol Dis 73: 38-44, 2018.
60. Shi Q, Huo N, Wang X, Yang S, Wang J and Zhang T: Exosomes from oral tissue stem cells: Biological effects and applications. Cell Biosci 10: 108, 2020.
61. Zhao Z, Ji M, Wang Q, He N and Li Y: Circular RNA Cdr1as Upregulates SCAI to suppress cisplatin resistance in ovarian cancer via miR-1270 suppression. Mol Ther Nucleic Acids 18: 24-33, 2019.
62. Luo Y and Gui R: Circulating Exosomal circMYC is associated with the recurrence and bortezomib resistance in patients with multiple myeloma. Turk J Haematol 37: 248-262, 2020.
63. Ding C, Yi X, Wu X, Bu X, Wang D, Wu Z, Zhang G, Gu J and Kang D: Exosome-mediated transfer of circRNA CircNFIX enhances temozolomide resistance in glioma. Cancer Lett 479: 1-12, 2020.
64. Anantha RW, Simhadri S, Foo TK, Miao S, Liu J, Shen Z, Ganesan S and Xia B: Functional and mutational landscapes of BRCA1 for homology-directed repair and therapy resistance. Elife 6: e21350, 2017.
65. Yang X, Fraser M, Abedini MR, Bai T and Tsang BK: Regulation of apoptosis-inducing factor-mediated, cisplatin-induced apoptosis by Akt. Br J Cancer 98: 803-808, 2008.
66. Shang J, Chen WM, Liu S, Wang ZH, Wei TN, Chen ZZ and Wu WB: CircPAN3 contributes to drug resistance in acute myeloid leukemia through regulation of autophagy. Leuk Res 85: 106198, 2019.
67. Liu Y, Dong Y, Zhao L, Su L and Luo J: Circular RNA-MTO1 suppresses breast cancer cell viability and reverses monastrol resistance through regulating the TRAF4/Eg5 axis. Int J Oncol 53: 1752-1762, 2018.
68. Wu T, Wang MC, Jing L, Liu ZY, Guo H, Liu Y, Bai YY, Cheng YZ, Nan KJ and Liang X: Autophagy facilitates lung adenocarcinoma resistance to cisplatin treatment by activation of AMPK/mTOR signaling pathway. Drug Des Devel Ther 9: 6421-6431, 2015.
69. Jiang B, Yan LJ and Wu Q: ABCB1 (C1236T) polymorphism affects P-glycoprotein-mediated transport of methotrexate, doxorubicin, actinomycin D, and etoposide. DNA Cell Biol 38: 485-490, 2019.
70. Huang MS, Yuan FQ, Gao Y, Liu JY, Chen YX, Wang CJ, He BM, Zhou HH and Liu ZQ: Circular RNA screening from EIF3a in lung cancer. Cancer Med 8: 4159-4168, 2019.
71. Su Y, Yang W, Jiang N, Shi J, Chen L, Zhong G, Bi J, Dong W, Wang Q, Wang C and Lin T: Hypoxia-elevated circELP3 contributes to bladder cancer progression and cisplatin resistance. Int J Biol Sci 15: 441-452, 2019.
72. Ping L, Jian-Jun C, Chu-Shu L, Guang-Hua L and Ming Z: High circ_100053 predicts a poor outcome for chronic myeloid leukemia and is involved in imatinib resistance. Oncol Res: Feb 14, 2019 (Epub ahead of print).
73. Joseph NA, Chiou SH, Lung Z, Yang CL, Lin TY, Chang HW, Sun HS, Gupta SK, Yen L, Wang SD and Chow KC: The role of HGF-MET pathway and CCDC66 cirRNA expression in EGFR resistance and epithelial-to-mesenchymal transition of lung adenocarcinoma cells. J Hematol Oncol 11: 74, 2018.
74. Kotmakçı M, Çetintaş VB and Kantarcı AG: Preparation and characterization of lipid nanoparticle/pDNA complexes for STAT3 downregulation and overcoming chemotherapy resistance in lung cancer cells. Int J Pharm 525: 101-111, 2017.
75. Garofalo M and Croce CM: MicroRNAs as therapeutic targets in chemoresistance. Drug Resist Updat 16: 47-59, 2013.
76. Sang Y, Chen B, Song X, Li Y, Liang Y, Han D, Zhang N, Zhang H, Liu Y, Chen T, *et al*: circRNA_0025202 regulates tamoxifen sensitivity and tumor progression via regulating the miR-182-5p/FOXO3a axis in breast cancer. Mol Ther 27: 1638-1652, 2019.
77. Reshke R, Taylor JA, Savard A, Guo H, Rhym LH, Kowalski PS, Trung MT, Campbell C, Little W, Anderson DG and Gibbings D: Reduction of the therapeutic dose of silencing RNA by packaging it in extracellular vesicles via a pre-microRNA backbone. Nat Biomed Eng 4: 52-68, 2020.
78. Liang Y, Song X, Li Y, Su P, Han D, Ma T, Guo R, Chen B, Zhao W, Sang Y, *et al*: circKDM4C suppresses tumor progression and attenuates doxorubicin resistance by regulating miR-548p/PBLD axis in breast cancer. Oncogene 38: 6850-6866, 2019.
79. Yang W, Gu J, Wang X, Wang Y, Feng M, Zhou D, Guo J and Zhou M: Inhibition of circular RNA CDR1as increases chemosensitivity of 5-FU-resistant BC cells through up-regulating miR-7. J Cell Mol Med 23: 3166-3177, 2019.
80. Yu W, Peng W, Sha H and Li J: Hsa_circ_0003998 promotes chemoresistance via modulation of miR-326 in lung adenocarcinoma cells. Oncol Res 27: 623-628, 2019.
81. Shang J, Chen WM, Wang ZH, Wei TN, Chen ZZ and Wu WB: CircPAN3 mediates drug resistance in acute myeloid leukemia through the miR-153-5p/miR-183-5p-XIAP axis. Exp Hematol 70: 42-54.e3, 2019.
82. Kun-Peng Z, Xiao-Long M, Lei Z, Chun-Lin Z, Jian-Ping H and Tai-Cheng Z: Screening circular RNA related to chemotherapeutic resistance in osteosarcoma by RNA sequencing. Epigenomics 10: 1327-1346, 2018.
83. Liu F, Zhang J, Qin L, Yang Z, Xiong J, Zhang Y, Li R, Li S, Wang H, Yu B, *et al*: Circular RNA EIF6 (hsa_circ_0060060) sponges miR-144-3p to promote the cisplatin-resistance of human thyroid carcinoma cells by autophagy regulation. Aging (Albany NY) 10: 3806-3820, 2018.
84. Gao D, Qi X, Zhang X, Fang K, Guo Z and Li L: hsa_circRNA_0006528 as a competing endogenous RNA promotes human breast cancer progression by sponging miR-7-5p and activating the MAPK/ERK signaling pathway. Mol Carcinog 58: 554-564, 2019.
85. Zhou Y, Zheng X, Xu B, Chen L, Wang Q, Deng H and Jiang J: Circular RNA hsa_circ_0004015 regulates the proliferation, invasion, and TKI drug resistance of non-small cell lung cancer by miR-1183/PDPK1 signaling pathway. Biochem Biophys Res Commun 508: 527-535, 2019.
86. Hua X, Sun Y, Chen J, Wu Y, Sha J, Han S and Zhu X: Circular RNAs in drug resistant tumors. Biomed Pharmacother 118: 109233, 2019.
87. Xiong W, Ai YQ, Li YF, Ye Q, Chen ZT, Qin JY, Liu QY, Wang H, Ju YH, Li WH and Li YF: Microarray analysis of circular RNA expression profile associated with 5-fluorouracil-based chemoradiation resistance in colorectal cancer cells. Biomed Res Int 2017: 8421614, 2017.
88. Zhu KP, Zhang CL, Ma XL, Hu JP, Cai T and Zhang L: Analyzing the interactions of mRNAs and ncRNAs to predict competing endogenous RNA Networks in osteosarcoma Chemo-Resistance. Mol Ther 27: 518-530, 2019.
89. Chi BJ, Zhao DM, Liu L, Yin XZ, Wang FF, Bi S, Gui SL, Zhou SB, Qin WB, Wu DM and Wang SQ: Downregulation of hsa_circ_0000285 serves as a prognostic biomarker for bladder cancer and is involved in cisplatin resistance. Neoplasma 66: 197-202, 2019.
90. Wu G, Sun Y, Xiang Z, Wang K, Liu B, Xiao G, Niu Y, Wu D and Chang C: Preclinical study using circular RNA 17 and micro RNA 181c-5p to suppress the enzalutamide-resistant prostate cancer progression. Cell Death Dis 10: 37, 2019.