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Recent advances in the contribution of circRNAs to cisplatin chemotherapy resistance in cancers

Minireview

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Worldwide, cancer is a serious threat to the health of citizens of every country, with the incidence and mortality increasing year by year. Cisplatin is the first-line anticancer drug commonly used in clinics and is widely used for the treatment of solid tumors including lung, gastric, liver, bladder, and ovarian cancer. Although cisplatin-based chemotherapy has a high clinical response efficacy, patients will inevitably develop drug resistance after repeated use, leading to severe restrictions of its application. Circular RNAs (circRNAs) are a promising class of non-coding RNAs capable of promoting or suppressing cancer via functioning as miRNAs sponges. Recently, an increasing amount of evidence shows that circRNAs are closely related to the cisplatin resistance of cancers. Therefore, standing at the perspective of the cisplatin chemotherapy resistance, this paper reviews the research progress of circRNAs related to cisplatin resistance of various cancers.

Key words: circular RNA, cisplatin, chemotherapy, resistance, cancer

The International Agency for Research on Cancer (IARC) has online released the newest global cancer statistics (https://www.iarc.who.int/faq/latest-global-cancer-data-2020-qa/) in 2020, providing the data that represents current national estimates of the latest incidence, mortality, and development trend of 36 cancer types in 185 countries. In 2020, there are 19.29 million new cases and 9.96 million deaths. Compared with the statistics reported in 2018 [1], the number of new cases increased by 6.6% and deaths by 3.8%. Among various cancers, lung cancer still ranks the first as a cause of cancer death. With the incidence and mortality of cancer increasing yearly, cancer is a serious threat to the health of every citizen around the world.

Cisplatin (CDDP) is a metal anticancer drug most commonly used in clinics. Its anticancer mechanisms can be listed as follows: firstly, CDDP forms intrastrand cross-links in DNA between adjacent purine residues, and induces a conformational alteration in DNA [2], thereby keeping RNA polymerase II (RNAP II) from DNA transcription and leading to cell death [3]; secondly, acting as mediators or enhancers of CDDP-triggered cytotoxicity, proteins containing high-mobility group (HMG) domains protect the intrastrand cross-link from cellular repair [4]; thirdly, certain proteins are believed to bind the DNA site damaged by CDDP. For example, when Sp1 (a sequence-specific Zn finger protein) binds to DNA, it aggravates DNA bending to enhance the damage [5]. Platinum drugs interfere with DNA to establish a good mode of effect. In addition, they may also interfere with RNA. However, whether such interference effect serves as an activator to enhance anticancer and/or contributes to harmful side effects remains to be investigated [6]. Generally, CDDP-based chemotherapy is extensively employed against a wide spectrum of solid tumors including lung, gastric, and bladder cancers owing to its high clinical response efficacy and ability to prolong the survival of patients [7]. But cancer is prone to develop drug resistance after repeatedly using CDDP. The mechanisms of resistance mainly are that the eukaryotic RNAP II blocked at a site of DNA damage triggers the NER repair pathway [3] and that NER proteins, associated with CDDP-DNA adducts, are highly expressed by cancer cells to reduce the damage of platinum drugs [4]. Moreover, many cancers display resistance to CDDP by decreasing the

absorption of CDDP or increasing its efflux [8]. So, even if these cancers were initially sensitive to CDDP, they would eventually bloom into drug resistance, bringing about severe restrictions on the application of CDDP.

Circular RNAs (circRNAs), a class of non-coding RNAs, are characterized by covalently connecting free 3'- to 5'-ends, forming a closed circular structure [9]. This structure protects circRNAs from the degradation of ribonuclease, making them more stable than linear RNAs. CircRNAs widely exist in various tissues of the human body and their biological functions are dependent on their cell location. Cytoplasm-located circRNAs mainly act as competing endogenous RNA (ceRNA) to combine with microRNAs (miRNAs), and negatively regulate miRNAs expression. In other words, circRNAs adsorb miRNAs as a sponge [10–13]. In the past, researches on circRNAs mainly focused on their relationship with the malignant development of cancer. But in recent years, more and more studies have paid attention to the relationship between circRNAs and cancer radiotherapy and chemotherapy resistance [10, 14], which is of great significance for the treatment of cancer. In view of this, standing at the perspective of CDDP chemotherapy resistance, this paper reviews the research progress of circRNAs related to CDDP resistance of various cancers (Table 1).

Lung cancer

Lung cancer (LC) is the most common cancer in the world, with high morbidity and mortality. LC is histologically divided into two types: small cell lung cancer and non-small cell lung cancer (NSCLC). NSCLC is the most common type, accounting for about 80–85% of all LC cases [15]. Although the treatment plan is constantly being optimized, CDDP is still the first-line chemotherapeutic agent [16]. A study found that circAKT3 was highly expressed in clinical tissues and cells and regulated the expression of STAT3 by targeting miR-516b-5p, which in turn regulated the sensitivity of LC cells to CDDP [17]. circZFR was aberrantly upregulated in NSCLC tissues and cells, which regulated Cbl proto-oncogene like 1 (CBLL1) by targeting miR-545-3p, thereby protecting NSCLC cells against the damage induced by CDDP [18]. hsa_circRNA_103809 was highly expressed in LC resistant cell lines (A549/DDP, H1299/DDP, and Calu-3/DDP), and it negatively regulated miR-377-3p to promote the expression of glutamate oxaloacetate transaminase 1 (GOT1), leading to CDDP resistance in NSCLC cells [19]. The circ_0007385 is derived from host gene *MEMO1* and has been confirmed to be upregulated in NSCLC tissues and cells. It was found by molecular mechanism research that circ_0007385 upregulated high-mobility group box 1 (HMGB1) expression by sponging miR-519d-3p, contributing to the CDDP resistance [20]. circ-PRMT5, originated from the gene *PRMT5*, upregulated protein reversionless 3-like (REV3L) via targeting miR-4458 to promote CDDP resistance. Silencing of circ-PRMT5 improved the response rate of A549/DDP and H460 to CDDP [21]. circRNA_100565 was upregulated in CDDP-resistant NSCLC tissues and cells, and regulated indirectly the expression of ADAM metallopeptidase domain 28 (ADAM28) by sponging miR-377-3p to enhance the CDDP resistance of NSCLC cells [22]. hsa_circ_0014235 is derived from S100 calcium binding protein A2 (S100A2), and its expression was significantly increased not only in NSCLC tissues and cells but in exosomes from the serum of NSCLC patients. hsa_circ_0014235 overexpression enhanced the proliferation, migration, invasion, and CDDP resistance of NSCLC through upregulating the expression of cyclin-dependent kinase 4 (CDK4) by inhibiting miR-520a-5p [23]. Similarly, circ_PIP5K1A, derived from the *PIP5K1A* gene, was also upregulated in NSCLC tissues, serum, and cells. circ_PIP5K1A positively regulated the expression of ATP binding cassette subfamily C member 1 (ABCC1) through acting as a sponge for miR-101. ABCC1 is relevant to multidrug resistance, which promotes drug resistance by mediating the exclusion of chemotherapeutic drugs [24]. Compared with CDDP-sensitive NSCLC cells, circRNA CDR1as (CDR1as) and Homeobox protein Hox-A9 (HOXA9) were up-expressed, while miR-641 was down-expressed in CDDP-resistant cells. In *in vivo* and *in vitro* experiments, CDR1as positively regulated HOXA9 expressions by sponging miR-641 to reinforce tolerance to CDDP [25]. Additionally, experiments *in vitro* found that CDR1as promoted cancer stem cells (CSCs) enrichment and positively regulated cell stemness to facilitate the formation of drug resistance [25]. This means that it may be a potential approach to eliminate CSCs by targeting the CDR1as/miR-641/HOXA9 axis in CDDP resistant NSCLC cells. However, the study needs to be further verified by xenograft animal models *in vivo*.

The immune microenvironment is crucial for the development of NSCLC. Programmed death ligand-1 (PD-L1) is proved to not only mediate the immune escape but also regulate the drug resistance of cancer cells [26]. circ-CPA4 and PD-L1 were highly expressed, while let-7 miRNA (let-7) was lowly expressed in NSCLC tissues and cells. Patients with lower levels of circ-CPA4 and PD-L1 and higher let-7 tend to have a better prognosis. The experiment has demonstrated the regulation mechanism between circ-CPA4, let-7, and PD-L1, which is that circ-CPA4 regulates the PD-L1 expression by targeting let-7. Moreover, PD-L1 exosomes derived from NSCLC cells also self-regulate cell stemness to enhance the CDDP resistance of NSCLC cells [26].

circ_0076305 was upregulated in NSCLC tissues and cells, which acted as a sponge of miR-296-5p to promote the expression of STAT3 to enhance the resistance of NSCLC cells to CDDP [27]. circ-ABCB10 was overexpressed in NSCLC cells and sponged miR-556-3p to upregulate adenylate kinase 4 (AK4) by serving as a ceRNA *in vitro*, making LC cells tolerable to CDDP damage [28]. circCCND1, confirmed to be upregulated in NSCLC cells and patients, could interact with miR-187-3p to regulate the expression of reactive

Table 1. circRNAs related to cisplatin resistance.

Cancer	circRNA	Upregulated/ Downregulated	miRNA	Factor	Model
Lung cancer	circAKT3	upregulated	miR-516b-5p	STAT3	*in vitro* and *in vivo*
	circZFR	upregulated	miR-545-3p	CBLL1	*in vitro* and *in vivo*
	hsa_circ_103809	upregulated	miR-377-3p	GOT1	*in vitro* and *in vivo*
	circ_0007385	upregulated	miR-519d-3p	HMGB1	*in vitro* and *in vivo*
	circ-PRMT5	upregulated	miR-4458	REV3L	*in vitro* and *in vivo*
	circRNA_100565	upregulated	miR-377-3p	ADAM28	*in vitro* and *in vivo*
	hsa_circ_0014235*	upregulated	miR-520a-5p	CDK4	*in vitro* and *in vivo*
	circ_PIP5K1A*	upregulated	miR-101	ABCC1	*in vitro* and *in vivo*
	circRNA CDR1as	upregulated	miR-641	HOXA9	*in vitro* and *in vivo*
	circ-CPA4*	upregulated	let-7	PD-L1	*in vitro* and *in vivo*
	circ_0076305	upregulated	miR-296-5p	STAT3	*in vitro*
	circ_ABCB10	upregulated	miR-556-3p	AK4	in vitro
	circCCND1	upregulated	miR-187-3p	ROS, FGF9	*in vitro*
	hsa_circ_0085131	upregulated	miR-654-5p	ATG7	*in vitro*
	circ_0008928*	upregulated	miR-488	HK2	*in vitro*
	circPVT1	upregulated	miR-145-5p	ABCC1	*in vitro*
	circRNA CDR1as	upregulated	unclear	EGFR	*in vitro*
	hsa_circ_0046264	upregulated	unclear	unclear	*in vitro*
	hsa_circ_0096157	upregulated	unclear	unclear	*in vitro*
	circ-SMARCA5	downregulated	unclear	unclear	*in vitro*
	hsa_circ_0001946	downregulated	unclear	unclear	*in vitro*
	circEIF3as	unclear	unclear	unclear	in vitro
	circ_0000079#	downregulated	unclear	FXR1	*in vitro*
Gastric cancer	circFAM73A	upregulated	miR-490-3p	HMGA2	*in vitro* and *in vivo*
	hsa_circ_0081143	upregulated	miR-646	CDK6	*in vitro* and *in vivo*
	circAKT3	upregulated	miR-198	PIK3R1	*in vitro* and *in vivo*
	circDONSON	upregulated	miR-802	BMI1	*in vitro* and *in vivo*
	circPVT1	upregulated	miR-152-3p	HDGF	*in vitro* and *in vivo*
	circVAPA	upregulated	miR-125b-5p	STAT3	*in vitro* and *in vivo*
	circPVT1*	upregulated	miR-30a-5p	YAP1	*in vitro* and *in vivo*
	circ_0110805	upregulated	miR-299-3p	ENDOPDI	*in vitro* and *in vivo*
	circCCDC66	upregulated	miR-618	BCL2	*in vitro* and *in vivo*
	circMCTP2	downregulated	miR-99a-5p	MTMR3	*in vitro* and *in vivo*
	circCUL2	downregulated	miR-142-3p	ROCK2	*in vitro* and *in vivo*
	circ_0000260*	upregulated	miR-129-5p	MMP11	*in vitro* and *in vivo*
	circ_0026359	upregulated	miR-1200	POLD4	*in vitro*
	circFN1	upregulated	miR-182-5p	unclear	*in vitro* and *in vivo*
Liver cancer	circARNT2	upregulated	miR-155-5p	PDK1	*in vitro* and *in vivo*
	circRNA_102272	upregulated	miR-326	RUNX2	*in vitro* and *in vivo*
	circ_PRMT5	upregulated	miR-924	POU3F2	*in vitro* and *in vivo*
	circRNA_101505	downregulated	miR-103	NOR1	*in vitro* and *in vivo*
	circ_0003418	downregulated	unclear	β-catenin	*in vitro* and *in vivo*
	circRNA_101237	upregulated	unclear	unclear	*in vitro*
	circ-SMARCA5	downregulated	unclear	unclear	*in vitro*
Osteosarcoma	circTADA2A	upregulated	miR-129-5p	TRPS1, YAP1	*in vitro* and *in vivo*
	circUBAP2	upregulated	miR-506-3p	SEMA6D	*in vitro*
	circ-LARP4	downregulated	miR-424	unclear	*in vitro*
	circPVT1	upregulated	unclear	ABCB1	*in vitro*
	circ_001569	upregulated	unclear	p-GSK3β, β-catenin	*in vitro*
	hsa_circ_103801*	upregulated	unclear	unclear	*in vitro*

Table 1. ***Continued ...***

Cancer	circRNA	Upregulated/ Downregulated	miRNA	Factor	Model
Bladder cancer	circFNTA	upregulated	miR-370-3p	FNTA	*in vitro* and *in vivo*
	circRNA CDR1as	downregulated	miR-1270	APAF1	*in vitro* and *in vivo*
	circELP3	upregulated(hypoxia)	unclear	unclear	*in vitro* and *in vivo*
	hsa_circ_0000285	downregulated	unclear	unclear	*in vitro*
	circLIFR#	downregulated	no	MSH2	*in vitro* and *in vivo*
Ovarian cancer	circHIPK2	upregulated	miR-338-3p	CHTOP	*in vitro* and *in vivo*
	circRNA CDR1as*	downregulated	miR-1270	SCAI	*in vitro* and *in vivo*
	circFoxp1*	upregulated	miR-22, miR-150-3p	CEBPG, FMNL3	*in vitro* and *in vivo*
Colorectal cancer	circ_0071589	upregulated	miR-526b-3p	KLF12	*in vitro* and *in vivo*
	circ_0020095	upregulated	miR-487a-3p	SOX9	*in vitro* and *in vivo*
			miR-338-3p	Met	*in vitro*
Cervical cancer	circMTO1	upregulated	miR-6893	S100A1, Beclin1, p62	*in vitro* and *in vivo*
	hsa_circ_0023404	upregulated	miR-5047	VEGFA	*in vitro*
Oral squamous cell carcinoma	circ_0109291	upregulated	miR-188-3p	ABCB1	*in vitro* and *in vivo*
	circ_0001971	upregulated	miR-194, miR-204	unclear	*in vitro* and *in vivo*
Laryngeal carcinoma	circPGAM1	upregulated	miR-376a	ATG2A	*in vitro* and *in vivo*
	circ_0004507	upregulated	miR-873	MRP1, MDR1	*in vitro* and *in vivo*
Thyroid carcinoma	circEIF6	upregulated	miR-144-3p	TGF-α	*in vitro* and *in vivo*
Esophageal cancer	circRNA_001275	upregulated	miR-370-3p	Wnt7a	*in vitro*
Nasopharyngeal carcinoma	hsa_circ_0028007	upregulated	unclear	unclear	*in vitro*

Note: *research involving exosomes; #circRNAs combined with proteins

oxygen species (ROS) and fibroblast growth factor 9 (FGF9), serving as a promoter for drug resistance of NSCLC treated with CDDP [29]. hsa_circ_0085131 is derived from poly(A) binding protein cytoplasmic 1 (PABPC1) that encodes polyadenylate binding protein, and it was upregulated in CDDP resistant NSCLC tissues and cells. hsa_circ_0085131 sponges miR-654-5p to elevate the expression of autophagy related 7 (ATG7), which triggers autophagy and promotes CDDP resistance [30]. circ_0008928 was obviously upregulated in serum exosomes of CDDP-resistant NSCLC patients and CDDP-resistant NSCLC cells. circ_0008928 was a sponge of miR-488 which bound to hexokinase 2 (HK2), and circ_0008928 silencing improved the CDDP sensitivity [31]. circPVT1, derived from the *PVT1* gene, was highly expressed in lung adenocarcinoma (LAD) tissues and cells. It regulated ABCC1 expression by targeting miR-145-5p and participated in the resistance of CDDP and pemetrexed chemotherapy [10]. Likewise, Lu *et al.* [32] detected the levels of serum circPVT1 in NSCLC patients who received CDDP combined with gemcitabine chemotherapy and found the expression of circPVT1 in the chemotherapy resistance group was higher than that in the sensitive group, suggesting that circPVT1 was related to chemotherapy resistance. Therefore, the effect of chemotherapy may be determined by the level of circPVT1 in serum.

In chemotherapy-resistant LAD cells, silencing of CDR1as reduced IC50 of pemetrexed (PTX) and CDDP, which showed that silencing of CDR1as made resistant LAD cells re-sensitive to PTX and CDDP. The mechanism might be that CDR1as activated the EGFR/PI_3K signaling pathway. However, whether CDR1as acts as ceRNA to sponge certain miRNA remains to be further discussed [33]. hsa_circ_0046264, elevated in LC tissues, promoted the proliferation, migration, and invasion of A549 cells, and significantly aggravated drug resistance [34]. But still, more research is required to clarify the mechanisms in detail. Developed by the ligation of long non-coding RNA MALAT1, the overexpression of hsa_circ_0096157 was found to promote the resistance of NSCLC cells to CDDP [35]. It is noticeable that the result disclosed novel mechanisms for long non-coding RNA to regulate tumorigenesis and drug resistance for the first time. circ-SMARCA5, derived from the *SMARCA5* gene, was downregulated in NSCLC cells and its upregulation enhanced the chemotherapy sensitivity by functioning as a tumor suppressor [36]. However, the miRNA/target protein axis related to it remains unclear. The expression level of hsa_circ_0001946 was low in LC tissues and cells, especially in CDDP-resistant cells. Downregulation of hsa_circ_0001946 decreased cell apoptosis and CDDP sensitivity, but the specific mechanisms leading to drug resistance are still unclear. It may regulate the NER signaling pathway through four potential miRNAs (hsa-miR-7-5p, hsa-miR-671-5p, hsa-miR-1270, or hsa-miR-3156-5p) [15].

One newly released research shows that a variety of circEIF3as have been detected in drug-sensitive and drug-resistant LC cells, among which hsa_circ_0004350 and hsa_circ_0092857 were differentially expressed [37]. Downregulation of hsa_circ_0004350 and hsa_circ_0092857

may affect the resistance of LC cells to CDDP [37]. Nevertheless, the potential mechanisms are still unclear. Another new study shows that hsa_circ_0081664, hsa_circ_0081666, and hsa_circ_0013502 may play a role in the CDDP resistance of NSCLC, yet their expression levels in clinical tissues, functions, and mechanisms are still at an unknown stage [7].

Gastric cancer

Although methods such as molecularly targeted therapy have emerged, surgical resection and adjuvant chemotherapy are still the main means for gastric cancer (GC) treatment [13]. For patients who have been pathologically diagnosed with advanced GC and have not received chemotherapy, chemotherapy based on CDDP and fluorouracil is regarded as the first-line treatment. But patients always develop resistance after several courses of chemotherapy [12]. circFAM73A was elevated in GC tissues, and functions as a sponge of miR-490-3p to modulate HMGA2 (High mobility group A2) expression to enhance the CDDP resistance of GC. Moreover, HMGA2 could further promote circFAM73A expression, generating a positive feedback regulation [38]. hsa_circ_0081143 was highly expressed in GC tissues and regulated the expression of cell division protein kinase 6 (CDK6) by targeting miR-646, which in turn affected the sensitivity of GC cells to CDDP [39]. circAKT3 was upregulated in tissues from CDDP-resistant GC and in CDDP-resistant cells. Mechanistically, circAKT3 sponges miR-198 to abolish the suppressive effect of the miRNA on its downstream target gene *PIK3R1*, which activated the PI_3K/Akt signaling pathway in GC cells, finally upregulating the DNA repair molecule breast cancer type 1 susceptibility protein (BRCA1) and promoting CDDP-resistance [12]. circDONSON, derived from back-splicing of DONSON mRNA, was upregulated in CDDP-resistant GC tissues and cells, and it regulated the expression of B lymphoma Mo-MLV insertion region 1 (BMI1) protein by targeting miR-802 to affect the tolerance of GC cells to CDDP [40]. circPVT1 was upregulated in CDDP-resistant GC tissues and cells, and it promoted the expression of hepatoma-derived growth factor (HDGF) by acting as a sponge for miR-152-3p, thereby activating the PI_3K/Akt signaling pathway to induce drug resistance [41]. circVAPA was upregulated in clinical GC tissues, and regulated STAT3 by sponging miR-125b-5p to modulate the CDDP resistance in GC progression [42]. Besides, Yao *et al.* [43] found that circPVT1 was highly expressed in exosomes from CDDP-resistant GC serums and cells and that circPVT1 promoted the resistance to CDDP through the miR-30a-5p/YAP1 axis. circ_0110805 was detected to be upregulated in GC tissues and cells and was higher in the CDDP-resistant ones. circ_0110805 elevates the expression of endothelial protein disulfide isomerase (ENDOPDI) by targeting miR-299-3p to weaken the sensitivity of GC to CDDP [44]. circCCDC66, originating from the *CCDC66* gene, was upregulated in the CDDP-resistant GC tissues and cells and it plays a role in boosting CDDP resistance through the miR-618/BCL2 axis [45]. BCL2 acts as an oncogene in cancer due to its anti-apoptotic effect. However, the specific mechanisms of how it regulates the resistance of GC cells to CDDP are still under study.

Abnormally activated autophagy induced by chemotherapeutic drugs provides energy for cancer cells, thus promoting resistance of GC cells to CDDP [13]. MTMR3, one of the members of the myotubularin family, is an inositol lipid 3-phosphatase that hydrolyzes PI3P to inhibit the formation of autophagosomes. In the CDDP-resistant GC cells and tissues, the expression of circMCTP2 was downregulated, suppressing the expression of MTMR3 by targeting miR-99a-5p. The continuous decrease of the MTMR3 level triggered the formation of autophagosomes and promoted the resistance of GC to CDDP [46]. circCUL2, the product of back-splicing of the CUL2 mRNA, was downregulated in both GC tissues and cells. ROCK2, a serine-threonine kinase that regulates the morphology and migration of cells, was significantly increased in the CDDP-resistant cells overexpressing circCUL2. circCUL2 regulates CDDP sensitivity through autophagy induced by miR-142-3p/ROCK2 [13].

Gastric adenocarcinoma (GAC) is the main subtype of GC, most of which were diagnosed as advanced, and coupled with the drug resistance, the prognosis of the patients is unsatisfactory [47]. circ_0000260 was highly expressed in GAC-derived tissues and serum exosomes and was more abundant in the CDDP-resistant group than in the sensitive group. circ_0000260 promoted the expression of matrix metalloproteinase 11 (MMP11) by targeting miR-129-5p, triggering GAC resistance to CDDP [47]. circ_0026359 was mainly overexpressed in the cytoplasm of GC cells with the CDDP resistance and it regulated the expression of DNA polymerase δ subunit 4 (POLD4) by targeting miR-1200 to enhance the CDDP resistance [48]. The expression level of circFN1 was elevated in the CDDP-resistant GC samples and cells. High expression circFN1 inhibited miR-182-5p and removed this miRNA from inducing the apoptosis via the caspase-3 signaling pathway, and weakened CDDP-induced apoptosis [49]. circFN1 affected the sensitivity of cells to CDDP by targeting miR-182-5p but it is unclear whether there is a direct binding site between miR-182-5p and caspase-3. Therefore, the specific mechanisms of miR-182-5p regulating apoptosis and the effect of this apoptosis under the mechanism on CDDP resistance should be deeply studied.

Liver cancer

The tissue type of most patients with primary liver cancer is hepatocellular carcinoma (HCC). Although HCC can be treated by transplantation, surgical resection, radiofrequency ablation (RFA), transarterial chemoembolization (TACE), and systemic chemotherapy, the treatment of advanced

HCC is still very limited. CDDP-based chemotherapy is the main effective method to control the development of HCC and prolong patients' life, but repeated chemotherapy makes many patients respond poorly to CDDP [50, 51]. A study shows that 538 circRNAs were significantly upregulated and 430 downregulated in CDDP-resistant HCC tissues compared with CDDP-sensitive tissues [50]. circARNT2 was upregulated in HCC tissues and cells, and it regulated 3-phosphoinositide dependent protein kinase-1 (PDK1) by targeting miR-155-5p to make HCC cells resistant to CDDP [50]. The expression of circRNA_102272 was significantly upregulated in HCC tissues and cells, especially in CDDP-resistant cell lines. circRNA_102272 regulated the expression of RUNX2, a member of runt-related transcription factors, by targeting miR-326 to promote the CDDP-resistance of HCC [52]. circ_PRMT5 increased the expression of POU3F2, a POU-homeodomain transcription factor, by targeting miR-924 to regulate the progression and CDDP-resistance [53]. Interestingly, circ_PRMT5 not only regulated the expression of MRP1 and P-gp through the miR-924/POU3F2 axis but also participated in regulating signal transduction of the Wnt/β-catenin/c-Myc pathway through the axis in CDDP-resistant HCC cells [53]. Therefore, the future challenges are to determine the detailed relationship of these new regulatory networks.

Downregulation of circRNA_101505 was related to the poor survival of HCC. It upregulated oxidored-nitro domain-containing protein 1 (NOR1) by targeting miR-103 to display tumor suppressor effect and overexpression of circRNA_101505 made HCC cells re-sensitive to CDDP *in vitro* and *in vivo* [54]. In HCC tissues and cells, the expression level of circ_0003418 was detected to be reduced, which mediated the adjustment of CDDP sensitivity by affecting the expression of β-catenin and c-Myc [51]. *c-Myc* is one of the downstream target genes of the Wnt signaling pathway [55]. So, it is speculated that the regulation of c-Myc by circ_0003418 may be achieved via the Wnt/β-catenin pathway but whether circ-0003418 acts as a sponge of some miRNA needs to be further discussed. In addition, circRNA_101237 was elevated in tumor tissues and serum samples of patients with HCC, especially in CDDP-resistant HCC patients and cells [56]. However, whether circRNA_101237 knockdown will enhance the CDDP-sensitivity of HCC cells is still unclear, and more research is needed to reveal its underlying molecular mechanisms.

Intrahepatic cholangiocarcinoma (ICC) is the second most common type, and its incidence has increased in the last 20 years. Surgical resection is the cornerstone of treatment of ICC but chemotherapy is beneficial to improve the clinical efficacy. circ-SMARCA5 was downregulated in the ICC tissues and was related to good clinicopathological characteristics and survival status. Upregulation of circ-SMARCA5 improved the chemosensitivity of ICC cells to CDDP and gemcitabine [57] but its underlying molecular mechanism is currently unclear.

Osteosarcoma

Osteosarcoma (OS) is a common malignant bone tumor that mainly affects adolescents. At present, the treatment is mainly surgical resection, supplemented by radiotherapy and chemotherapy [58, 59]. Although CDDP and other anticancer drugs bring benefits to patients, drug resistance may also lead to treatment failure [60]. Yes-associated protein (YAP) and Trichorhinophalangeal syndrome 1 (TRPS1) were upregulated in various OS cell lines and positively correlated with circTADA2A. But compared with other OS cell lines, the U2OS line exhibited the highest expression of YAP1, while MG63 showed the highest level of TRPS1. TRPS1 mainly contributes to drug resistance. Both YAP1 and TRPS1 were targets of miR-129-5p, which was the target of circTADA2A. That is to say, circTADA2A enhanced the expression of YAP1 and TRPS1 by regulating miR-129-5p to promote the proliferation and drug resistance of OS cells [59]. It is noteworthy that circTADA2A expression in MG63 was lower than in U2OS, which suggests that TRPS1 in MG63 cells may be regulated by other circRNAs to display strong drug resistance. Another study found that circUBAP2 was upregulated in CDDP-resistant OS tissues and cells. circUBAP2 promoted the expression of semaphorins 6D (SEMA6D) by targeting the tumor suppressor miR-506-3p, and then SEMA6D activated the Wnt/β-catenin signaling pathway to stimulate the resistance of OS to CDDP [60].

circ-LARP4, a tumor suppressor, was down-expressed in tumor tissues and acted as a sponge of miR-424 to improve the sensitivity of OS cells to CDDP and adriamycin. circ-LARP4, as one of the transcripts of the *LARP4* gene, directly or indirectly regulated the expression of LARP4 protein but it is unclear whether there is a direct binding site between LARP4 and miR-424 [58]. circPVT1 was highly expressed in OS tissues and cells, especially in the groups with lung metastasis or chemoresistance and in multidrug resistant OS cell lines. circPVT1 knockdown partly reversed the resistance of OS cells to adriamycin and CDDP *in vitro*. The mechanisms may be that circPVT1 acts as a certain miRNA sponge to regulate the expression of ATP-binding cassette sub-family B member 1 (ABCB1), which can enhance chemotherapy resistance through pumping out the intracellular drugs by the P-gp protein [61]. However, bioinformatics analyses combined with a dual-luciferase reporter system are required to further search for related miRNAs. circ_001569 was significantly overexpressed in OS tissues compared with adjacent non-cancerous bone tissues, and it activated the Wnt/β-catenin signaling pathway to promote the resistance of OS cells to CDDP [62]. Exosome-mediated circRNAs transfer is another mechanism of CDDP resistance of OS. Pan *et al.* [63] found hsa_circ_103801 was significantly higher in the serum exosomes from OS patients than that in the serum exosomes from healthy controls. The higher expression of hsa_circ_103801 in serum exosomal was correlated with shorter survival in OS patients. hsa_

circ_103801 overexpression reinforced the CDDP resistance but the involved miRNA and downstream target molecules are still unclear.

Bladder cancer

When diagnosed with bladder cancer (BC), about 75% of patients are non-muscle-invasive BC (NMIBC) and 25% muscle-invasive BC (MIBC). NMIBC patients have a lifelong risk of recurrence, of which 10–20% will develop to MIBC after surgery, while those with MIBC are at high risk for metastasis after radical cystectomy [64]. Once BC runs to an advanced stage, the only treatment option is chemotherapy combined with CDDP but drug resistance is the main factor limiting the long-term survival of BC patients [65, 66]. BC is related to the sex hormones and their receptors, such as the androgen receptor (AR). AR suppresses RNA editing genes *ADAR2* to accelerate the expression of circFNTA in diverse BC cell lines. Then, circFNTA transmits the signal from AR to FNTA through miR-370-3p, which in turn activates KRAS to enhance the aggressiveness and CDDP resistance of BC [64]. Upregulated CDR1as in T24 and EJ cells was negatively correlated to the survival rates of cells at different CDDP concentrations, and CDR1as enhanced the sensitivity of BC cells to CDDP by regulating the expression of apoptosis protease-activating factor 1 (APAF1) via targeting miR-1270 [66]. Under hypoxia, the capacity of proliferation and drug resistance of BC cells were improved. Silencing circELP3, spliced from the *ELP3* gene, could reduce proliferation and CDDP resistance of BC cells to the level that healthy BC cells were under normoxia. Also, tumor growth *in vivo* was suppressed by interfering with the expression of circELP3 [65]. This effect indicates the important role of cirELP3 in hypoxia-induced tumor development. In addition, hsa_circ_0000285 was downregulated in tissues and serums from BC patients and its expression was lower in CDDP-resistant BC [67]. However, the specific regulatory mechanisms of either cirELP3 or hsa_circ_0000285 need to be studied more deeply.

Ovarian cancer

The 5-year overall survival rate of ovarian cancer (OC) is between 35–40% and the main factor limiting the long-term survival of patients is the CDDP resistance [68]. A study found that there are 148 circRNAs upregulated and 191 downregulated in CDDP-resistant tissues of OC [68]. Among them, circHIPK2 was highly expressed in OC patients' serum, tissues, and OC cells, and higher expression was discovered in CDDP-resistant OC tissues and cells. circHIPK2 regulated chromatin target of protein arginine methyltransferase (CHTOP), a novel modulator in CDDP resistance of OC, by targeting miR-338-3p, and circHIPK2 knockdown suppressed CDDP resistance of OC [69]. CDR1as was decreased in CDDP-resistant tissues and cells, which affected the sensitivity to CDDP by regulating the expression of suppressor of cancer cell invasion (SCAI) via serving as a sponger of miR-1270. Interestingly, CDR1as was detected in serum exosomes of patients with OC, and its expression level in the patients with CDDP resistance was lower than those with CDDP sensitivity [68]. Luo *et al.* [70] found that circFoxp1 was significantly increased in circulating exosomal from patients with epithelial ovarian cancer (EOC). circFoxp1 overexpression diminished the sensitivity of CDDP, while circFoxp1 knockdown enhanced the chemotherapy efficacy. The mechanism may be that circFoxp1 regulates the expression of CCAAT enhancer binding protein gamma (CEBPG) and formin like 3 (FMNL3) by miR-22 and miR-150-3p. Exosomes are nanoscale lipid bilayer vesicles released to the extracellular space through exocytosis. They can be secreted out of cells by almost all types of cells under various physiological and pathological conditions. Exosomes carrying circRNAs have high stability and tissue specificity [70]. Therefore, CDR1as and circFoxp1 in exosomes may be the markers for diagnosing OC and judging the level of drug resistance.

Colorectal cancer

CDDP-based chemotherapy is commonly employed for the treatment of colorectal cancer, but the acquired drug resistance may limit the success of therapy [71]. circ_0071589 was upregulated in CDDP-resistant colorectal cancer tissues and cells, and it targeted and inhibited miR-526b-3p expression to regulate Krüppel-like factor 12 (KLF12). circ_0071589 knockdown intensified CDDP-induced reduction of xenograft tumor growth in nude mice [71]. circ_0020095 was abundantly expressed in colon cancer tissues and cells, and it regulated the expression of SRY-box transcription factor 9 (SOX9) by targeting miR-487a-3p to affect the sensitivity of colon cancer cells to CDDP. What's more, circ_0020095 was confirmed to regulate Met expression by miR-338-3p [72], which suggests that circ_0020095 may target various miRNAs to promote tumorigenesis in colon cancer and is a potentially effective intervention target.

Cervical cancer

CDDP is proved to be one of the most effective chemotherapeutic agents for advanced or recurrent cervical cancer (CC), but its efficacy and clinical application are also affected by frequent drug resistance [73]. A study demonstrated that circMTO1 was upregulated in CC tissues and cells, and it regulated S100A1 by targeting miR-6893. Depletion of circMTO1 suppressed the migration, invasion, and chemotherapy resistance of CC cells. Also, circMTO1 changed the expression level of autophagy-related proteins (elevated the expression of Beclin1 and reduced the level of p62) through miR-6893 to enhance the CDDP resistance [74]. Guo *et al.* [75] found that hsa_circ_0023404 was upregulated in CC

cells and it increased the expression of Vascular endothelial growth factor A (VEGFA) by targeting miR-5047, which promoted the metastasis and CDDP resistance. They also found that hsa_circ_0023404 inhibited autophagy to promote the chemotherapy resistance of CC. Autophagy is the process that cells degrade damaged and unnecessary cellular components (such as damaged organelles and proteins) through lysosomes. In lung and gastric cancer, autophagy was proved to strengthen the resistance of cancer cells to CDDP. However, there is no definite conclusion on whether autophagy plays a role in enhancing or inhibiting the CDDP resistance in CC cells, and more experiments are needed to clarify it.

Oral squamous cell carcinoma

Many adverse prognostic reactions in patients with oral squamous cell carcinoma (OSCC), such as metastasis or recurrence, are related to CDDP resistance [76]. circ_0109291 was upregulated in OSCC tissues and cells, especially in CDDP-resistant tissues and cells, and it regulated the expression of ABCB1 by targeting miR-188-3p [77]. circ_0001971 was upregulated in OSCC tissues and cells, which suppressed the expression of miR-194 and miR-204 to boost the CDDP resistance of cancer cells [76]. But it is unclear which are the downstream target molecules of miR-194 and miR-204.

Laryngeal carcinoma

Advanced laryngeal carcinoma is prone to drug resistance to CDDP-based chemotherapy. Recently, circPGAM1 and circ_0004507 have been identified, which are essential for the CDDP resistance of laryngeal carcinoma. In laryngeal carcinoma tissues, the expression of circPGAM1 and circ_0004507 were increased. circPGAM1 regulates autophagy-related gene *ATG2A* by acting as a sponge of miR-376a to affect the sensitivity of laryngeal carcinoma cells to CDDP [78], while circ_0004507 is the sponge of miR-873. A study indicated that circ_0004507 knockdown elevated the expression of miR-873 and weakened the tolerance to CDDP *in vivo* [79]. Mechanistically, circ_0004507/miR-873 may regulate the expression of multidrug resistance-related proteins (MRP1 and MDR1) to contribute to chemoresistance [79]. Controlling the expression of circ_0004507 may be an effective treatment for CDDP-resistant patients with laryngeal carcinoma.

Other types of cancer

Among thyroid carcinoma, papillary thyroid carcinoma (PTC) is the most common type, while anaplastic thyroid carcinoma (ATC), also known as undifferentiated carcinoma, is rare but the most malignant [80]. circEIF6 were primarily identified in PTC tissues. The high expression of circEIF6 regulated the expression of TGF-α by acting as a sponge of the miR-144-3p, thereby activating the autophagy to promote CDDP resistance in PTC and ATC cells [80]. Furthermore, circRNA_001275 was upregulated in CDDP-resistant esophageal cancer tissues and cells, and it regulated the expression of Wnt7a, one of Wnt ligands, by targeting miR-370-3p, contributing to the resistance of esophageal cancer to CDDP [81]. Dong *et al.* [82] found that silencing hsa_circ_0028007 elevated the sensitivity of poorly differentiated NPC cell lines (CNE2 and HONE1) to paclitaxel and CDDP in nasopharyngeal carcinoma. Nonetheless, the specific mechanisms are still unclear and they need to be further verified in cell models carrying a high level of hsa_circ_0028007 and experiments relevant to animal models.

Discussion

CDDP is a widely used anticancer drug, which is very effective for many solid tumors. But due to the powerful DNA repair capacity of cancer cells, patients, especially in the final stage of the disease, often develop drug resistance. Clinicians are forced to increase the dosage for CDDP resistance, which will lead to aggravation of the system toxicity. For a long time, scholars are trying to use other drugs to replace CDDP. For example, the anticancer activity of ruthenium compounds is similar to CDDP but the number of ruthenium-DNA complexes is significantly lower than platinum drugs. Thus, anticancer activity, scope, and systemic toxicity of ruthenium compounds are less than platinum compounds [83–85]. Copper complexes seem to be a potential anticancer agent, which triggers cancer cell death through apoptosis or paraptosis mechanisms, and at the same time, they are able to avert serious side effects, as endogenous copper is believed to be less toxic to normal cells [86]. Other metals (such as rhodium, iridium [87]), like copper, have also shown anticancer activity *in vitro*. Some researchers proposed adding platinum compounds to aromatic residues so that metal residues could be firmly anchored to nucleic acids through the insertion of aromatic groups, which was conducive to the effect of metal on nucleic acid bases. But actually, the platinum-containing residues prevent full penetration of the aromatic residues so that only a partial insertion is formed [88, 89]. Compared with CDDP, the hybrid of estradiol and platinum compounds is more effective and stable in uterine cancer cell lines but it is also more cytotoxic than CDDP [90]. Therefore, the hybrid may have more serious side effects than CDDP. Ji *et al.* [8] constructed a new specific nanomedicine carrier for CDDP, which not only improved the utilization of CDDP but also reduced toxicity. Also, another study showed that solid lipid nanoparticles, which carry a plasmid encoding anti-STAT3 short hairpin RNA, could improve the chemotherapy sensitivity of cancers by suppressing the expression of STAT3 [91]. The abovementioned unfold the powerful potential of metal drugs and nanotechnology in the treatment of cancer. However, whether nano-drugs complexes may reduce the drug resistance of some tumor cells that are naturally highly resistant to CDDP (such as NSCLC)

needs to be further studied. Nanotechnology is expected to provide better treatments for patients with cancer, especially for those who are resistant to CDDP, yet these studies were verified only *in vitro*. In summary, although patients with malignancy may develop the CDDP-resistance during the process of chemotherapy, CDDP is still the current first-line chemotherapeutic agent for clinical treatment and is in an irreplaceable position. This means that patients receiving CDDP-based treatments may inevitably suffer from CDDP resistance. Therefore, improving sensitivity is one of the current methods to solve this problem.

With the rapid development of high-throughput sequencing technology, more and more circRNAs have been screened and identified. According to the cell location of circRNAs, they are divided into nuclear circRNAs and cytoplasmic circRNAs. Previous studies manifested that nuclear circRNAs play a role in regulating the transcription of parental genes, while cytoplasmic circRNAs act as miRNA sponges. Since most circRNAs are mainly found in the cytoplasm, sponge adsorption is the most important function [9, 45]. Nevertheless, emerging evidence shows that the unique covalent closed loop structure and specific tertiary structure of circRNAs may not only act as a miRNA sponger but also may combine with certain proteins to promote drug resistance. For example, circ_0000079 was significantly decreased in tissues from NSCLC patients, especially in drug-resistant patients. Its overexpression could decoy fragile X-related 1 (FXR1), an RNA binding protein, to interrupt the formation of the FXR1/PRCKI (protein kinase C, iota) complex to reduce the invasiveness and drug resistance of NSCLC cells [92]. Evidence indicated that circLIFR, located in the nucleus, was significantly downregulated in BC. circLIFR could combine with MMR genes MutS homolog 2 (MSH2) to form an RNA-protein complex, governing CDDP chemotherapy efficacy [93]. Recently, a study showed that there was an internal ribosome entry site (IRES), open reading frame (ORF), and m6A modification in the structure of circPVRL3, which provided potential capabilities for circPVRL3 to encode proteins. However, these amazing functions of circRNAs are still unknown and need to be further explored [27]. It can be seen from Table 1 that CDR1as was upregulated in LC but downregulated in bladder and ovarian cancer. In both two types of cancers, CDR1as acts as a sponger for miR-1270, yet the downstream target molecules of miRNA are not the same. In addition, circPVT1 was elevated in a variety of cancers (such as lung, gastric, and osteosarcoma) but the involving target molecules are different. Consequently, circRNAs regulatory mechanisms are diverse and have a momentous effect on the CDDP resistance of various cancers. circRNAs broadly exist in eukaryotes, both abundant and stable. circRNAs, which are not only expressed differently in disparate diseases but also easy to obtain, are suitable to be the biomarkers and intervention targets for tumor diagnosis and treatment, and for monitoring prognosis. For instance, CDR1as is an independent prognostic marker for patients with LAD [33]. Higher circ-SMARCA5 expression can independently predict disease-free survival and overall survival of NSCLC patients [36]. circRNA_101237 is an independent predictor of prognosis of HCC patients [56], while circFoxp1 in circulating exosomes is an independent predictor of survival outcome and CDDP resistance in EOC patients [70].

Apart from drug resistance, CDDP clinical application is limited by its side effects, mainly nephrotoxicity [94]. circRNAs also play an important part in CDDP-induced acute kidney injury (AKI). The latest research elucidated that the expression of circ-0114427 was increased in different early-stage AKI models, and it upregulated the expression of activating transcription factor 3 (ATF3) by combining with miR-494 to reduce downstream inflammatory factors, playing a protective role in the early development of inflammation [95]. As a result, circ-0114427 may be used as a potential molecule to diagnose the early stage of AKI. Its decline may become a warning to guide clinicians to recognize the aggravation of inflammatory damage as soon as possible and respond timely to the renal toxicity induced by CDDP.

In summary, circRNAs contribute to the regulation of CDDP chemotherapy resistance and the treatment aimed at circRNAs may improve CDDP resistance. circRNAs may be used to monitor drug response to help clinicians to screen suitable drugs and formulate individualized plans or act as molecular targets for developing new treatment methods. Exploring and identifying CDDP-related circRNAs is of great value for cancer precise treatments. In order to reveal deeply the nature of circRNAs, future researches on circRNAs should be focused on the causes of their shear formation and upstream regulation mechanisms.

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