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The emerging role of circular RNAs in cisplatin resistance in ovarian cancer: From molecular mechanism to future potential

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ABSTRACT

Ovarian cancer (OC) is the most common cause of death in female cancers. The prognosis of OC is very poor due to delayed diagnosis and identification of most patients in advanced stages, metastasis, recurrence, and resistance to chemotherapy. As chemotherapy with platinum-based drugs such as cisplatin (DDP) is the main treatment in most OC cases, resistance to DDP is an important obstacle to achieving satisfactory therapeutic efficacy. Consequently, knowing the different molecular mechanisms involved in resistance to DDP is necessary to achieve new therapeutic approaches. According to numerous recent studies, non-coding RNAs (ncRNAs) could regulate proliferation, differentiation, apoptosis, and chemoresistance in many cancers, including OC. Most of these ncRNAs are released by tumor cells into human fluid, allowing them to be used as tools for diagnosis. CircRNAs are ncRNA family members that have a role in the initiation, progression, and chemoresistance regulation of various cancers. In the current study, we investigated the roles of several circRNAs and their signaling pathways on OC progression and also on DDP resistance during chemotherapy.

1. Introduction

Ovarian cancer (OC) has the highest cancer-related mortality rate among female gynecological cancers and is the fifth leading cause of death among all women [1–3]. OC is generally referred to as a group of diseases, which are classified into three types based on their histological origin, including epithelial, germ cell, and specialized stromal cell tumors [4]. The most common sub-type of OC is epithelial ovarian cancer (EOC), which is also the most lethal gynecological cancer worldwide [5]. Diagnosis of OC in the early stages is difficult due to its invasive growth pattern; therefore, more than 70 % of patients with OC are in advanced stages of the disease at the time of diagnosis [6,7].

The prognosis of OC is very poor due to the delayed diagnosis, high metastatic frequency, lack of effective treatment for the recurrence, and chemo-resistance of OC [2,3,6]. Surgical tumor excision in conjunction with systemic chemotherapy is the primary treatment for OC; however, alternative treatments, including hormone therapy, radiotherapy, and immunotherapy are also employed [8]. Depending on the stage of the

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disease, the approach differs. The staging of OCs is based on surgical and pathological findings in early-stage disease. Total abdominal hysterectomy and bilateral salpingo-oophorectomy are generally curative for low-risk endometrial cancer patients [9]. In advanced stages, surgical resection of the tumor mass, debulking, or cytoreductive surgery is followed by intravenous (IV) platinum/taxane-based chemotherapy. Neoadjuvant chemotherapy (NACT), intraperitoneal (IP) chemotherapy, hyperthermic IP chemotherapy, and maintenance immunotherapy are also additional options to achieve a better outcome. NACT is the administration of chemotherapy before the primary debulking or cytoreductive surgery. A combination of Cisplatin/Carboplatin and Paclitaxel with Bevacizumab or Cyclophosphamide is used in regimens for NACT. It may improve the prognosis of subjects with advanced OC by reducing the morbidity of the primary surgery and decreasing the tumor volume before the surgery [10,11]. Hyperthermic IP chemotherapy (HIPEC) is another treatment strategy that is thought to increase the cytotoxicity via different mechanisms, such as increasing cellular uptake and improving the crosslinking to DNA [12]. Bevacizumab, a monoclonal antibody, is also another drug commonly used in specific regimes combined with platinum/taxane-based chemotherapy and as maintenance immunotherapy as well [13]. Different platinum/taxane-based regimens are used for IV/IP chemotherapy depending on the staging and residual tumor mass after cytoreduction surgery [11]. The current standard treatment approach for OC consists of tumor debulking surgery followed by platinum-based chemotherapy such as effective cisplatin (DDP) and carboplatin with a taxane-family drug such as paclitaxel or docetaxel [14].

DDP is a widely used chemotherapeutic drug in the treatment of a wide spectrum of cancers, such as ovarian, testicular, bladder, gastric, and lung cancer. DDP consists of a sterile saline solution that contains two molecules of chlorine and two molecules of chlorine ammonia linked to the platinum atom in a cis configuration [15]. DDP plays a multidirectional cytotoxic role in the induction of apoptosis by damaging DNA, activating several signal transductions, and then inhibiting replication and mitosis [16]. Although chemotherapy with DDP is effective in many OC patients, important drawbacks in treating cancer patients with DDP are its side effects, such as nephrotoxicity, ototoxicity, neurotoxicity, gastrointestinal toxicities, and the high recurrence of disease due to the acquired resistance to DDP after several cycles of chemotherapy [17–19]. Moreover, the occurrence of chemo-resistance has severe effects on the life quality of OC patients and the shortening of the chemotherapy window period and is known as an important and limiting factor in the long-term survival of these patients [20–23].

Resistance can occur in two ways: inherent (without previous contact with the drug) and acquired (as a result of previous contact with the drug) [24,25]. Variables involved in such a circumstance may include host variables (e.g., genetic variants and drug-drug interactions), tumor-related factors, and tumor-host interactions [26]. One of the tumor-related factors is the development of physical barriers to drugs. Other common mechanisms resulting in chemotherapy failure include the stimulation of biological processes promoting drug release or degradation, elevated EMT, enrichment of cancer stem cells (CSCs), and reduced apoptosis [27,28]. Most cytotoxic drugs act by inhibiting a specific signaling pathway, restoring the involved pathway, or activating collateral signaling cascades. Pathway-specific mechanisms in chemo-resistance include proliferative signaling cascades and DNA repair. Some tumors may also alter the structure of molecular networks, allowing them to coordinate tumor growth without requiring the related pathways [27,29]. OC has a high chance of developing resistance to DDP, especially in advanced stages [30]. The mechanisms involved in the occurrence of DDP resistance in OC include.

i) Reduced accumulation of DDP inside the cell via an increase in the level of ATP7A and ATP7B produced by DDP-resistant cells [31,32]. DDP is transported into the cell by copper transporters 1 and 2 (CTR1 and CTR2), while two copper-transporting ATPases 7A and 7B (ATP7A and ATP7B) transport DDP out of the cell, resulting in a decrease in the number of CTR1 and CTR2 [31,32].
ii) Intracellular inactivation of DDP by an increase in the level of nucleophilic biological elements (e.g., glutathione or metallothioneins) and their conjugation with DDP, reducing the cytotoxic activity of DDP in tumoral cells [19,24].
iii) Increased effectiveness of DNA damage repair (DDR) processes, including nucleotide excision repair (NER), mismatch repair (MMR), homologous recombination (HR), and nonhomologous recombination (NHR) [33]. NER is the most significant DDP process; it removes platinum DNA adducts formed by DDP through components such as ERCC1 and XPF [34]. The MMR pathway is another DDR system that corrects single-strand DNA mistakes. It is unable to totally repair the damage induced by DDP, resulting in apoptosis activation. In this process, DDP resistance can be caused by downregulation of the pathway via mutations or modifications in the promoters of related genes [35]. DDP resistance is also developed through the HR and NHR pathways by repairing the double-strand breaks in DNA caused by DDP, which create the most dangerous lesions [34].
iv) Inhibition of DDP-induced apoptotic processes involving the loss of functional p53 protein and upregulation of the antiapoptotic protein BCL-2 and proteins from the IAP family, which inhibit the activation of caspase [36].
v) Tumor microenvironment (TME) variables influencing treatment resistance are divided into two categories: physical and biological factors. Physical factors, such as tumor cell density and changes in the ECM, can interfere with DDP efficacy. The biological factor category comprises biochemical complications of cancer development, such as hypoxia and acidity, and normal cells, like stromal cells, tumor-associated fibroblasts, and immune cells [37], that are able to activate anti-apoptotic processes through the secretion of chemokines and also assist in the intracellular inactivation of DDP [34].
vi) Changes in the autophagy processes, cytoskeleton, and mitochondria are also known to be other mechanisms contributing to the development of DDP resistance. The induction of autophagy instead of apoptosis results in DDP resistance [19,25].
vii) Epigenetic modifications, which include DNA methylation, histone modifications, and non-coding RNA regulation, are thought to contribute to chemo-resistance via a variety of processes, including upregulation of multidrug resistance proteins (MRPs), remodeling of the tumor microenvironment, and dysregulation of the immune system [38,202].

According to recent studies, non-coding RNAs (ncRNAs), CSCs, immunological systems, autophagy, tumor heterogeneity, and tumor microenvironment (TME) all have a role in OC drug sensitivity [39–41]. Thus, these items can regulate cell growth, modify cell differentiation, control apoptosis, and develop chemo-resistant tumor cells [42]. Considering that different molecular mechanisms are involved in the development of DDP resistance in OC, it is necessary to know these mechanisms in order to obtain new therapeutic approaches.

NcRNAs are transcriptional RNAs that are classified into four categories: microRNA (miRNA), long ncRNA (lncRNA), circular RNA (circRNA), and PIWI-interacting RNA (piRNA) [18,43,203]. NcRNAs were initially identified as alternatively spliced errors that could not encode any proteins; nevertheless, as the study progressed, it was discovered that circRNAs encode small peptides. These translating "circRNA" have small open reading frames (sORFs) that could encode peptides with less than ten amino acids [44,45].

CircRNAs have a single-stranded structure that is synthesized through different mechanisms: a. splicing is usually accompanied by transcription by RNA polymerase II; b. transcription factors; and c. RBPs can inhibit or activate circRNA synthesis depending on the type of the

circRNA or the tissue [46–48]. It is believed that there are two main biogenesis mechanisms for circRNAs: lariat-driven circularization and intron-pairing-driven circularization or back splicing, which is the ligation of the downstream 5′ splicing site and the upstream 3′ splicing site [49,50]. During splicing, introns are removed and exons bond to each other. Most circRNAs contain two or three exons without intron segments. Meanwhile, some circRNAs contain only one exon that happens to have a longer length than those with multiple exons [51].The processes of splicing-dependent circRNAs include: 1. containing only intronic sequences (2′ → 5′-linked circular RNAs); 2. containing both exonic and intronic sequences (3′ → 5′-linked circular RNAs); and 3. containing only exonic sequences (3′ → 5′-linked circRNAs) [52] (Fig. 1). CircRNAs containing introns usually act within the nucleus, while those containing exons act in the cytoplasm. CircRNAs bind to RBPs and generate RNA protein complexes (RPCs), which are involved in a variety of biological processes [53,54]. A subset of RBPs influences circRNA synthesis by interacting with adjacent introns. Some move introns closer together, facilitating circularization [55,56], while others stabilize [57] or disrupt Alu pairs [58], promoting or inhibiting back-splicing. A new investigation revealed that circRNA synthesis is controlled by N6-methyladenosine (m6A). Depletion of methyltransferase-like 3 (METTL3) or YTH domain-containing 1 (YTHDC1) regulates roughly 20 % of certain types of circRNAs but has no substantial effect on linear transcripts [59]. A further study discovered that inhibiting alkB homolog 5 (ALKBH5) promotes the synthesis of translatable circRNAs by enriching m6A at junction locations. Additionally, YTHDF3 recognizes the m6A-modified initiation codon and launches translation [60]. Nonetheless, it is unknown whether there are any other regulators in which m6A localization influences the decision between back and canonical splicing.

Recently, studies revealed new information about the circRNA degradation process, which aids in the maintenance of a dynamic equilibrium. It has been shown that RNase L can totally destroy circRNAs. Endogenous circRNAs are often misfolded and suppress PKR, whereas their loss results in abnormal PKR activity and autoimmune disorders [61]. A further investigation revealed that YTHDF2 detects m6A-loading circRNAs and binds to RNase P/MRP in the mitochondria via heat-responsive protein 12 (HRSP12). CircRNAs are then destroyed by endoribonucleolytic enzymes [62]. A further investigation suggested another approach for regulating both mRNA and circRNA degradation by the interaction of RNA helicase and ATPase (UPF1) and stress granule assembly factor 1 (G3BP1) with extremely organized duplex areas [63]. Furthermore, miR-671 can regulate CDR1as degradation via Ago2 pathway [64]. GW182 (a critical element of the P-body and RNAi complex) also participates in circRNA decay [65]. More research is required to properly comprehend circRNA degradation processes and explain their balance and varied localization among cell types.

CircRNAs are stably generated in a variety of cell types, particularly in brain regions [66,67]. Scientists have also uncovered specific intron-loading circRNAs that are maintained in the chromosomes and influence the activity of their heritage genes [68,69]. Some Exon-derived circRNAs are also mainly localized in the nucleus, where they enhance protein storage [70] or transfer proteins to genome [71]. A recent study found that decreasing UAP56 or URH49 enables circRNAs

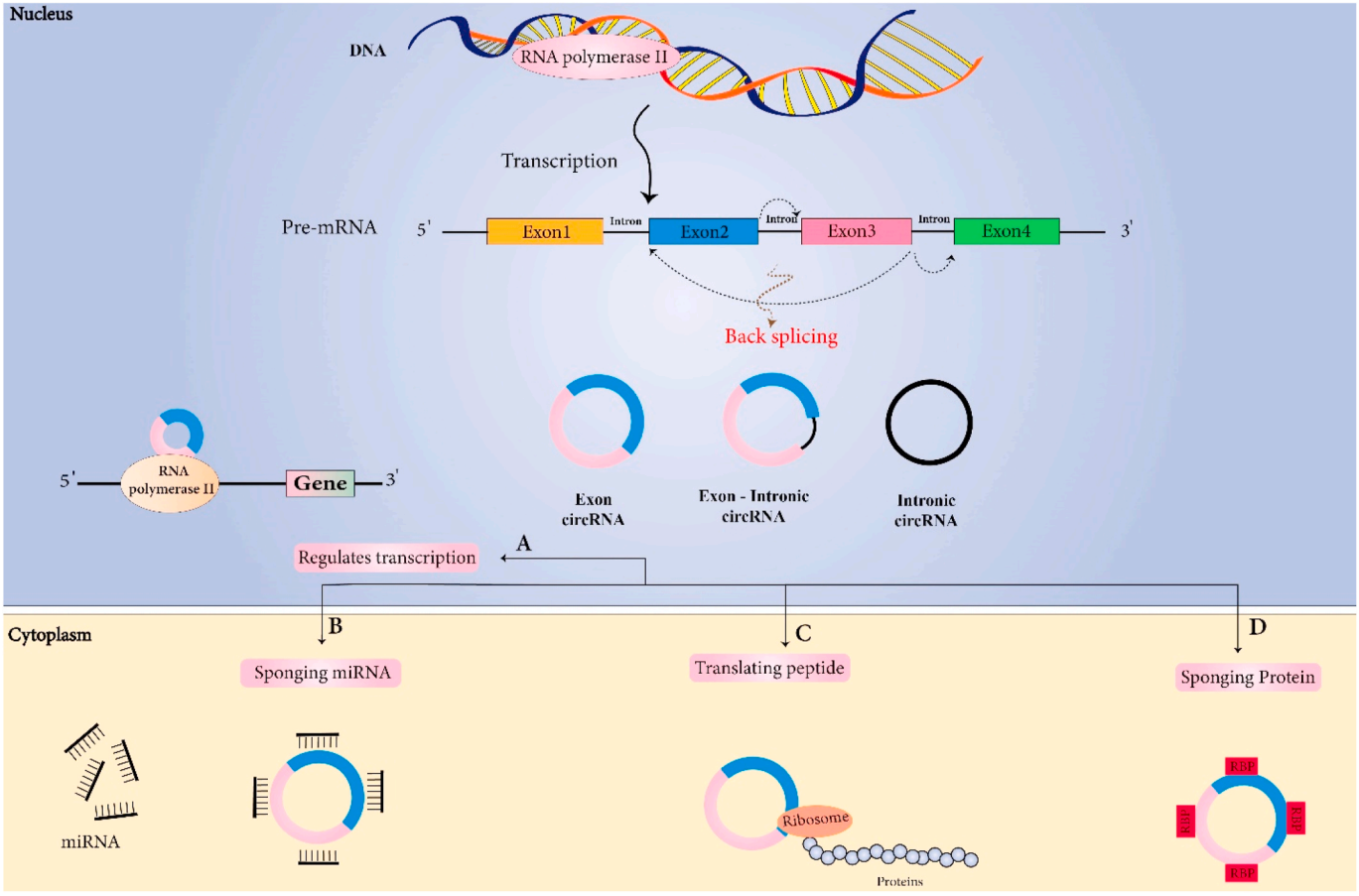

Fig. 1. A schematic view showing the biogenesis pathway of circRNAs. CircRNAs are generated through a non-canonical splicing process known as "backsplicing." This unique mechanism results in the formation of covalently closed circular transcripts, which can be classified as exonic, intronic, or a combination of both. CircRNAs can serve diverse roles include: A) regulate gene transcription by interacting with transcriptional regulatory factors, B) act as miRNA sponges, and thereby modulating the expression of their target genes, C) undergo translation to produce protein products and, D) bind to RNA-binding proteins (RBPs) and mediate their actions.

to cluster in the nucleus [72]. Another study discovered that YTHDC1 recruitment can control circNSUN2 nuclear transport, providing preliminary proof that m6A regulates circRNA export [73]. Furthermore, circRNAs can be distributed by extracellular vesicles (EVs) and identified in the bloodstream and urine [74]. The classification of these exosomal circRNAs appears to be controlled by source cells-related miR levels, whereas the exact physiological functions conveyed to target cells in various contexts remain unclear [75,76]. A few studies have recently found and studied mitochondria-located circRNAs, expanding our understanding of circRNA origin and mitochondrial transcript sequencing [77–79]. Nonetheless, circRNAs found in different organelles or subcellular spaces require additional examination.

Protein relocation is typically accompanied by increased or decreased activity, as well as facilitated or impaired exposure to targets, which results in increased or decreased functionalities and related downstream changes. A new study discovered that the mitochondrial-encoded circRNAs (mecciRNAs) mecciND1 and mecciND5 can act as chaperones to bind to the outer membrane translocase (mitochondrial M4040) and improve the entrance of replication protein A2 (RPA32) and hnRNPA1 into mitochondria. However, mecciRNAs can just support newly produced peptides in adopting conformations that facilitate mitochondrial delivery, with minimal effect on mature proteins [80]. MecciRNAs are found both inside and outside mitochondria and can move dynamically. PNPASE, a key mitochondrial RNA trafficking molecule, binds to most mecciRNAs and regulates their mitochondrial content [80]. Nevertheless, little research has been conducted on the link between protein trafficking and circRNAs.

CircRNAs, most likely due to their low abundance and high stability, are involved in long-term processes such as differentiation rather than highly dynamic ones such as cell proliferation or migration [81]. One of the key functions of circRNAs is to act as a microRNA sponge, which leads to the inhibition of miRNAs [82]. Multiple target sites for a specific miRNA have been detected in circRNAs [83]. CircsRNAs, as protein decoys, usually reverse their target protein's physiological action [46]. CircsRNAs could serve as scaffolds to facilitate protein-protein interplays, such as the interaction of circ-Foxo3 with CDK2 and p21 [82]. Although circRNAs are considered to have low protein-coding potential, many of them contain a start codon and an internal ribosomal entry site, which proves their unexpected potential for encoding proteins [84].

Unlike linear RNAs, circRNAs have a steady, conserved, covalent loop structure and are resistant to degradation by exonuclease in the cytoplasm due to having a unique continuous loop structure and not having 3′ and 5' ends [85]. Because of their high stability, circRNAs are known as biomarkers for diagnosis, prognosis, and prediction of response to treatment in body fluids (urine, plasma, exosomes, etc.) [86,87]. CircRNAs as post-transcriptional regulators can act by sponging miRNAs and competing with them to bind to the target mRNAs and/or RNA-binding proteins (RBPs) [88]. Several studies have shown that circRNAs contribute to pivotal physiological processes such as tumorigenesis, proliferation, invasion, metastasis, and chemoresistance in many types of cancer, including gastric cancer [89], colorectal cancer [90], hepatocellular carcinoma [91], and non-small cell lung cancer [92–94]. Accordingly, the circRNA-miRNA-mRNA regulatory pathway is crucial in cancer cell chemo-resistance [95,96].

Recent research has revealed that dysregulation of some circRNAs contributes to OC progression. For example, circRNA-MYKK increased cell growth in OC through the sequestration and inhibition of miR-652 [97]. Aberrant expression of circ_100395 increased OC cell growth and metastasis [98]. Circ-NOLC1 overexpression induced OC cell proliferation, migration, and invasion through interaction with the RNA-binding protein ESRP1 [99]. Also, increasing the expression of circ-Foxp1 is effective in accelerating cell proliferation and is DDP-resistant in OC cells [100]. Therefore, targeting circRNAs and elucidating their mechanisms may improve diagnostic and therapeutic strategies for OC. In the next sections, we described the biology and role of CircRNAs in DDP resistance in OC.

2. Relationship between circRNA expression and DDP resistance

OC treatment encountered restrictions due to chemoresistance processes. CircRNAs have been identified as a facilitating factor for tumor progression and chemoresistance. CircRNA upregulation of almost 148 circRNAs and downregulation of 191 circRNAs were seen in chemoresistant patients, implying that circRNAs have a significant function in the poor prognosis of OC [101]. Circ_0063804 is another circRNA with a high expression rate in OC cells. It promotes clusterin (CLU) protein expression by miR-1276 sponging. Circ_0063804 overexpression can also result in the up-regulation of p-glycoprotein (p-gp) and poly (ADP-ribosyl) polymerase (PARP) protein, as well as the down-regulation of cleaved PARP (c-PARP), which are responsible for the increase and inhibition of DPP resistance, respectively [51]. Circ_C20orf11 is also overexpressed in OC cells. The direct binding of circ_C20orf11 to the 3'-UTR of miR-527 leads to downregulation of miR-527. This competitive approach of circ_C20orf11 regulates YWHAZ expression, which is the direct target of miR-527. Finally, it suggests that overexpression of circ_C20orf11 leads to DDP resistance in OC cells [102]. Circ_0078607 was shown to be downregulated in DDP-resistant OC cells. Circ_0078607 overexpression sequesters miR-196b-5p and regulates GAS7 expression, which functions as a targeted cell arrest gene. As a result, overexpression of circ_0078607 sensitizes OC cells to DPP [103]. In the following section, we discussed in detail a variety of circRNAs involved in OC and the regulatory mechanisms of their effective signaling pathways on DDP chemo-resistance.

3. CircRNAs affect DDP resistance in ovarian cancer by targeting different mechanisms

Nowadays, among ncRNAs, circRNAs have gradually developed as a novel research hotspot and have attracted the attention of cancer researchers. Recent research indicates that circRNAs and a broad range of pathogenic processes (such as gene expression, cell proliferation, cell cycle, and drug resistance) have a close relationship in the case of OC. CircRNAs have the ability to target a wide range of molecules and molecular pathways; however, miRNAs have been identified as their main targets in numerous biological pathways. In the following, we discuss the circRNAs that regulate the DDP resistance mechanism in OC and underlying biological processes (Fig. 2 and Table 1).

3.1. *Circ-LPAR3 (circ_0004390)*

Circ_0004390 (also known as circ-LPAR3) has been found to be significantly elevated in OC tissue and is believed to have a key role in OC cell proliferation [104,105]. Circ_0004390 might serve as a sponge for miR-198, so that overexpression of circ_0004390 could downregulate the expression of miR-198. MiR-198 exerted an anti-tumor effect by suppressing the expression of the oncogene MET. Therefore, overexpression of circ_0004390 may boost the expression of the oncogene MET and lead to the development of OC [106]. In addition, circ_0004390 could decrease miR-634 expression in OC tissue. MiR-634 has the potential to attenuate the proliferation and progression of DPP-sensitive OC cells. Due to the decrease in miR-634 expression, the viability, growth, and DDP resistance of OC cells were triggered by pyruvate dehydrogenase kinase 1 (PDK1) overexpression. Therefore, circ_0004390 silencing could reduce tumor viability while intensifying DDP sensitivity by inhibiting the circ_0004390/miR-634/PDK1 pathway [107,108].

3.2. *Circ_0063804*

Circ_0063804 overexpression is related to the poor prognosis of OC patients. It could enhance tumor growth and decrease apoptosis. Similarly, circ_0063804 overexpression could promote DDP resistance and induce complications during treatment [109,110]. According to some

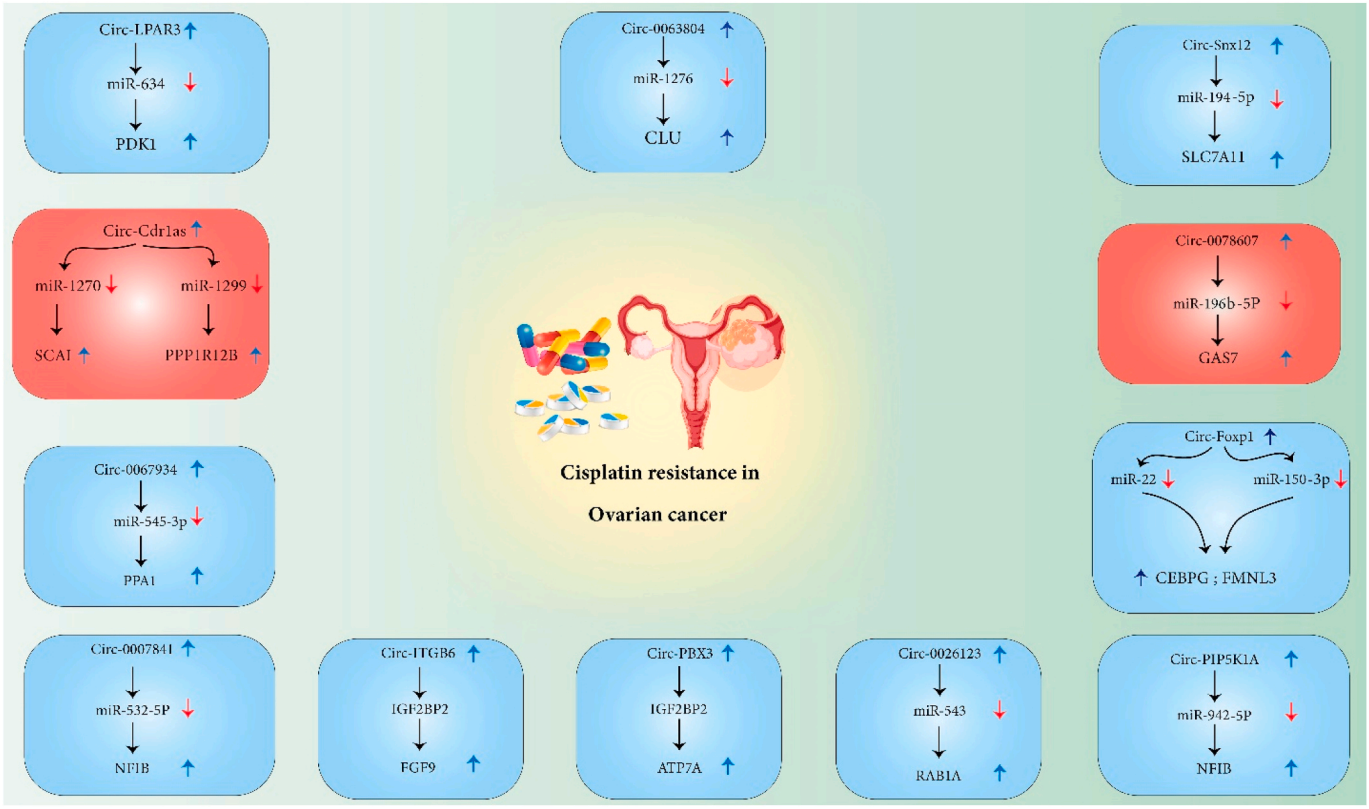

Fig. 2. Schematic representation of the interaction between circRNAs and the DDP resistance signaling pathway in OC progression. CircRNAs associated with DDP resistance signaling sponging miRNA targets and regulating their effects. Red squares indicate that the corresponding circRNA can suppress the DDP resistance (or induces the DDP sensitivity), while the blue squares show that the circRNA of interest may induce the DDP resistance.

research, p-gp and PARP contribute to DDP resistance, but c-PRAP is known as a DDP-resistance inhibitor [111–117]. Therefore, circ_0063804 silencing might promote OC cell apoptosis and hinder DDP resistance by downregulating p-gp and PARP. Moreover, it has been confirmed that circ_0063804 might act as a sponge for miR-1276, interfering with its action [51]. MiR-1276 exhibited anti-tumorigenic activity in a variety of malignancies, including breast cancer [118], bladder cancer [119], and gastric cancer [120]. You et al. have observed that miR-1276 sponging by circ_0063804 led to upregulation of CLU [51]. Overexpression of CLU is linked to limited OC progression due to inappropriate angiogenesis in the ME [121,122]. Also, CLU upregulation is related to DDP resistance in lung and bladder cancers [123,124]. Overall, circ_0063804 silencing could be considered a novel approach to obliterate DDP resistance and angiogenesis in OC.

3.3. Circ-Cdr1as (circ_0001946)

Circ-Cdr1as is another circRNA that has been discovered in several malignancies, including bladder cancer [125], nasopharyngeal carcinoma [126], and esophageal squamous cell cancer [127]. Wu et al. have stated that circ-Cdr1as had higher expression in DDP-sensitivity OC cell lines in comparison with DDP-resistance ones. In addition, they have figured out that circ-Cdr1 expression reduces proliferation, migration, and invasion while facilitating the apoptosis of OC cells. Circ-Cdr1as could also sponge for miR-1299 and increase the expression of the protein phosphatase 1 regulatory subunit 12B gene (PPP1R12B), a direct target of miR-1299. PPP1R12B was downregulated in DDP-resistance cancer cells, thus the CDR1as/miR1299/PPP1R12B axis might contribute to the chemosensitivity in OC [128]. In another study by Zhao et al., it was discovered that circ-Cdr1as functioned as a sponge for miR-1270, potentially reducing its activity as an inhibitor for the expression of the suppressor of cancer cell invasion (SCAI) gene. It has been observed that SCAI expression was higher in DDP-sensitive OC cells in comparison with DDP-resistance cells. So, circ-Cdr1as expression could enhance the DDP chemosensitivity of OC by increasing SCAI expression [101]. Altogether, the circ-Cdr1as/miR-1270/SCAI axis and the circ-CDR1as/miR1299/PPP1R12B axis could be considered novel approaches to the OC chemotherapy resistance problems.

3.4. Circ-Snx12

Ferroptosis is an oxidative, iron-dependent procedure of cell death that contains glutathione antioxidant inactivation, lipid peroxidation, and intracellular iron accumulation [129,130]. It has been discovered that ferroptosis is downstream of p53 and could act as a tumor suppressor [131,132]. Furthermore, ferroptosis might have a role in the attenuation of chemoresistance in some cancers, including OC [133–135]. Solute Carrier Family 7 member 11 (SLC7A11) could be considered a component for ferroptosis reduction by inducing glutathione synthesis. In other words, ferroptosis can be activated by SLC7A11 downregulation, which can enhance chemosensitivity [136, 137]. Qin et al. have indicated that SLC7A11 expression increased in DDP-resistance OC tissues. In addition, it has been shown that circ-Snx12 overexpression, which occurred in OC tissues, could enhance SLC7A11 expression through miR-194-5p sponging. Thus, DDP-sensitivity could be restored by circ-Snx12 knockdown, subsequently SLC7A11 downregulation, and then ferroptosis promotion [138].

3.5. Circ_0078607

It has been seen that circ_0078607 overexpression in DDP-resistant OC cells inhibits DDP resistance and cancer cell proliferation while also promoting cancer cell death. In addition, downregulation of

Table 1
CircRNAs and their targets in cisplatin-resistance of OC.

CircRNA	Dysregulation in OC	Corresponding Target/pathway	Effect on DDP resistance	Outcome	Ref
Circ-LPAR3 (circ_0004390)	Upregulation	Circ_0004390/miR-634/PDK1	DDP resistance enchantment	Silenced circ-LPAR3: ↑* Cell apoptosis Inhibited migration and invasion and proliferation	[108]
Circ_0063804	Upregulation	Circ_0063804/miR-1276/CLU	DDP resistance enchantment	↑ Proliferation ↓** Apoptosis of OC cells	[51]
Circ-Snx12	Upregulation	Circ-Snx12/miR194-5p/SLC7A11	DDP resistance enchantment	Silenced CircSnx12: ↓ Cell viability ↑ Ferroptosis	[138]
Circ_0067934	Upregulation	Circ_0067934/miR-545-3p/PPA1	DDP resistance enchantment	Silenced circ_0067934: ↓ Cell proliferation and invasion	[145]
circ_0007841	Upregulation	Circ_0007841/miR-532-5p/NFIB	DDP resistance enchantment	Silenced Circ_0007841: Inhibited cell proliferation, invasion, and migration, ↑ Cell apoptosis	[158]
Circ-Foxp1	Upregulation	CircFoxp1/miR-22 and miR-150-3p/ CEBPG and FMNL3	DDP resistance enchantment	Silenced circFoxp1: ↓ Cell proliferation	[100, 162]
Circ-ITGB6	Upregulation	CircITGB6/IGF2BP2/FGF9 RNA-protein complex	DDP resistance enchantment	Inducing the shifting of polarization TAM to M2 macrophages in the TME of the OC	[176]
Circ-PBX3	Upregulation	Circ-PBX3/IGF2BP2/ATP7A	DDP resistance enchantment	Reducing the efflux of DDP in OC cells ↑ Colony formation and tumor xenografts growth, ↓ Cell apoptosis	[177]
Circ_0026123	Upregulation	Circ_0026123/miR-543/RAB1A	DDP resistance enchantment	Silenced Circ_0026123: Suppressing cell growth, angiogenesis, invasion, and migration of OC cells	[181]
Circ-PIP5K1A	Upregulation	Circ-PIP5K1A/miR-942-5p/NFIB	DDP resistance enchantment	Silenced Circ-PIP5K1A ↓ Proliferation, migration, and invasion, ↑ Apoptosis	[190]
CircRNA	**Dysregulation in OC**	**Corresponding Target/pathway**	**Effect on DDP resistance**	**Outcome**	**Ref**
Circ-Cdr1as	Downregulation	Circ-CDR1as/miR-1270/SCAI Circ-CDR1as/miR1299/PPP1R12B	DDP resistance reduction	Overexpression of Cdr1as: Inhibited cell proliferation	[101, 128]
Circ_0078607	Downregulation	Circ_0078607/miR-196b-5p/GAS7	DDP resistance reduction	Overexpression of circ_0078607: ↑ Apoptosis of cancer cells via suppressing ABCB1, CyclinD1 and Bcl-2	[103, 104]

↑* indicates the elevation.
↓** indicates the reduction.
Abbreviations: NFIB; Nuclear factor I B, TME; Tumor microenvironment, OC; Ovarian cancer, PDK1; Phosphoinositide-dependent protein kinase-1.

circ_0078607 is associated with the unfavorable outcome of advanced-stage OC. Circ_0078607 directly sponged miR-196b-5p to increase growth arrest-specific 7 (GAS7) [104,139]. Several studies have pointed out the important role of MiR-196b-5p in a variety of cancers, such as acute myeloid leukemia [140], non-small cell lung cancer [141], colorectal cancer [142], and hepatocellular carcinoma [139]. Circ_0078607 and GAS7 overexpression increased the apoptosis rate of OC cells by hindering the functions of anti-apoptotic genes, including ABCB1, CyclinD1, and Bcl-2. According to the study by Dai et al., the circ_0078607 level was decreased in DDP-resistant OC cells, whereas Circ_0078607 increased the susceptibility of OC cells to DDP via the circ_0078607/miR-196b-5p/GAS7 axis, suggesting that it could be an appropriate candidate for the treatment of DDP-resistant OC cases [103, 104].

3.6. Circ_0067934

Circ_0067934 could act as an oncogene in hepatocellular carcinoma [143], bladder cancer [144], and gynecologic cancers, including OC [145], cervical cancer [146], and breast cancer [147]. Circ_0067934 upregulation in OC cells caused cancer cell proliferation, invasion promotion, and cell apoptosis reduction and is also linked to lymph node metastasis in the advanced stages of tumor. On the other hand, lowering circ_0067934 levels in OC cells resulted in a noticeable decrease in DDP resistance, cancer cell proliferation, and invasion. Circ_0067934 elevates inorganic pyrophosphatase 1 (PPA1) translation through miR-545-3p sponging [145]. PPA1 plays an important role in the synthesis of macromolecules such as nucleic acids, proteins, and carbohydrates, and its overexpression in OC cells increases cell survival by providing the energy required for rapid growth [148]. Moreover, PPA1 increases cell proliferation and invasion and also enhances the DDP resistance in OC cells by interacting with the phosphorylation of c-Jun N-terminal kinase (JNK), which can be used as a predictor of poor outcomes in OC patients [149,150]. JNK, as a stress-activated protein kinase, is a regulator of different cellular events. It has been observed that JNK1 inhibition contributes to cancer cell apoptosis and chemo-sensitivity enhancement [151]. Therefore, circ_0067934 could upregulate PPA1 expression via sequestration of miR-545-3p and then enhance tumor development and DDP resistance in OC by the JNK signaling pathway [145]. Therefore, circ_0067934 and PPA1 can be used as possible targets for reducing OC carcinogenesis and drug resistance in OC management, particularly in DDP-resistant OC.

3.7. circ_0007841

Exosomes are a type of extracellular vesicles and include metabolites, proteins, and nucleic acids that play significant roles in many biological processes, including cancer progression [152]. Studies have shown that DDP-resistant OC cells release exosomes containing circ_0007841. Circ_0007841 increased OC cell growth and was related to low survival rates, suggesting that it could be employed as a predictive biomarker in OC patients. Circ_0007841 could also serve as a sponge for miR-532-5p, an oncogene factor involved in breast cancer development [153], while acting as a tumor suppressor for glioma [154], lung cancer [155], and OC [156]. According to research, circ_0007841 suppressed tumors by upregulating the expression of nuclear factor I B (NFIB) as a result of miR-532-5p sponging [157,158]. NFIB binds to the DNA string, promotes cell metastasis through ameliorating chromatin accessibility, and also increases cell proliferation by targeting the Akt/Stat3 signaling pathway [159,160]. AKT is a proto-oncogene that is

involved in cancer cell proliferation, survival, and metabolism [161]. Gao et al. discovered that decreasing circ_0007841 expression increased OC cell susceptibility to DDP in vitro and in vivo by inhibiting cell proliferation, invasion, and migration and inducing cell apoptosis in DDP-resistant OC cells. Therefore, the circ_0007841/miR-531-5p/NFIB pathway can be considered a molecular mechanism to enhance DDP sensitivity in OC cells, and treating OC patients with DDP in conjunction with circ_0007841 inhibitors could be a novel approach in the treatment of DDP-resistant OC [158].

3.8. Circ-Foxp1

According to recent studies, the expression level of circ-Foxp1 as an oncogene was significantly increased in DDP-resistant OC. Moreover, circ-Foxp1 upregulation was related to cancer stage, early tumor size, metastasis, and clinical response to chemotherapy. Increasing circ-Foxp1 expression may improve cell growth and resistance to DDP in OC cells, whereas reducing circ-Foxp1 expression could decrease cell growth while increasing susceptibility to DDP in OC cells in vitro and in vivo. Circ-Foxp1 can also be used as a predictor of survival and disease recurrence in OC patients [100]. Circ-Foxp1 was potent to simultaneously serve as a sponge for both miR-22 and miR-150-3p and favorably influenced the expression of CCAAT enhancer binding protein gamma (CEBPG) and formin like 3 (FMNL3) [162]. CEBPG is a transcription factor that participates in physiological processes such as energy metabolism, tissue differentiation, and growth cell regulation [163]. Likewise, FMNL3 overexpression is related to cancer cell migration, invasion, metastasis, and poor prognosis in various cancers [164,165]. Several investigations have discovered that miR-22 and miR-150-3p act as tumor suppressors in a variety of tumors, including OC [166,167]. Therefore, overexpression of circ-Foxp1 and targeting miR-22 and miR-150-3p resulted in upregulation of CEBPG and FMNL3, increased proliferation, and decreased sensitivity of OC cells to DDP [100]. This finding suggested that suppressing the circ-Foxp1/miR-22 or miR-150-3p/CEBPG/FMNL3 axis would introduce a novel approach to enhancing DDP-sensitivity in OC cells.

3.9. Circ-ITGB6

Based on recent studies, it has been stated that cancer cells extensively interact with the TME to maintain proliferation, metastasis, and chemoresistance [168,201]. The TME of OC cells is highly immunosuppressive, and the predominant immune cells are macrophages. M1 macrophages have inflammatory and anti-tumor characteristics, while M2 macrophages have anti-inflammatory and tumor-promoting properties [169,170]. An increased proportion of M2 macrophages in the TME of OC cells is strongly related to tumor growth formation, tumor angiogenesis induction, chemoresistance promotion, and antitumor immune response suppression [171,172]. M2 macrophages can release some chemoprotective factors, including lysosomal enzymes and cathepsins B and S, in that way these type of macrophages can reduce the cytotoxicity of chemotherapy on tumor cells [173]. It has been indicated that circRNAs have potential to serve as a regulators of immune cells, including macrophages, natural killer cells, and $CD8^+$ T cells in the TME [174].

Li et al. observed that the expression level of hsa_circ_0056856 (circ-ITGB6) was increased in DDP-resistant OC patients and was associated with a poor prognosis[176]. Circ-ITGB6 improved the mRNA stability of fibroblast growth factor 9 (FGF9), a progression regulator of several malignancies through multiple pathological processes such as cancer cell proliferation and metastasis, by directly binding to insulin-like growth factor 2 mRNA-binding protein 2 (IGF2BP2) [175]. The formation of a circ-ITGB6/IGF2BP2/FGF9 RNA-protein complex contributed to shifting the polarization of tissue-associated macrophages (TAM) towards M2 macrophages and then induced DDP resistance in OC cells [176]. It has been observed that the expression level of circ-ITGB6 and FGF9 in DDP-resistant OC cells was higher than that of DDP-sensitive cells in vivo and in vitro, and circ-ITGB6 overexpression caused a significant increase in M2 macrophage-dependent DDP resistance. These results suggest that upregulation of circ-lTGB6 is associated with lower overall survival, higher relapse, and poor DDP response in OC patients [176]. Therefore, one of the major DDP-resistance processes in OC patients is the interaction between TAMs and cancer cells. A greater knowledge of the effective processes in this relationship can provide a clear perspective on the treatment of DDP-resistance OC patients.

3.10. Circ-PBX3

Circ-PBX3 is another circRNA with increased expression in DDP-resistant OC cells, which induces tolerance to DDP in vitro and in vivo. Circ-PBX3 can interact with IGF2BP2, which plays an important role in increasing mRNA stability. Therefore, circ-PBX3 overexpression increased ATP7A mRNA stability and ATP7A protein expression in OC cells through interaction with IGF2BP2 [177]. ATP7A (a member of P-type ATPase) is a copper efflux transporter that contributes to DDP efflux in cancer cells and brings resistance to DDP [178,179]. Fu et al. reported that the circ-PBX3/IGF2BP2 interaction enhanced ATP7A mRNA stability in OC cells. Thus, circ-PBX3 knockdown downregulated the ATP7A protein by lowering its stability [177]. Moreover, upregulation of the ATP7A protein is associated with a worse prognosis in OC patients undergoing chemotherapy with DDP [180]. Therefore, circ-PBX3 inhibition could be considered a therapeutic target to reduce ATP7A protein levels and then increase the sensitivity of OC cells to DDP.

3.11. Circ_0026123

Recent studies have shown that Circ_0026123 expression levels in DDP-resistant OC cells were greater than in DDP-sensitive cancer cells. Circ_0026123 could increase the expression of RAB1A (a member of the RAS oncogene family) through sponging miR-543. In other words, circ_0026123 overexpression reduced the expression of miR-543 and subsequently upregulated the RAB1A expression [181,182]. Increasing the expression of miR-543 and then RAB1A downregulation could inhibit cell growth and metastasis [183,184]. RAB1A is a small guanosine triphosphate (GTP) enzyme belonging to the Ras-associated binding (Rab) family, which plays an important role in the regulation of signal transduction, cell autophagy, and migration and also acts as an oncogene to promote the progression of multiple cancers [185,186]. Wei et al. indicated that circ_0026123 knockdown and RAB1A downregulation contributed to the suppression of cell growth, angiogenesis, invasion, and migration, as well as increasing the sensitivity of OC cells to DDP in vitro and in vivo [181]. These findings indicated that inhibition of the circ_0026123 expression level can be represented as a promising therapeutic target for combination therapy in DDP-resistant OC patients.

3.12. Circ-PIP5K1A

circ-PIP5K1A, also known as hsa_circ_0014130, is an oncogene that plays a substantial role in many cancers, including colon cancer [187], gastric cancer [188], and non-small cell lung cancer [189] by regulating malignant biological cell behavior. It has been observed that circ-PIP5K1A packaged in exosomes has the potential to transport from DDP-resistant OC cells to surrounding sensitive cells and mediate cell-to-cell communication. Sheng et al. discovered that circ-PIP5K1A and NFIB gene expression, which are the targets of MiR-942-5p, were higher in DDP-resistant OC cells than those with DDP-sensitive cells. While the expression of MiR-942-5p was decreased in DDP-resistant OC cells compared to DDP-sensitive cells, it could be understood that circ-PIP5K1A negatively regulates MiR-942-5p expression and subsequently upregulates NFIB expression [158,190,191]. Circ-PIP5K1A

induces DDP resistance in OC cells by suppressing miR-942-5p function on NFIB expression and upregulating NFIB expression. Downregulation of circ-PIP5K1A and subsequently NFIB could reduce cancer cell growth, progression, and invasion while enhancing the sensitivity to DDP in DDP-resistant OC cells in vitro and in vivo [104,190]. Thus, the circ-PIP5K1A/miR-942-5p/NFIB axis is involved in DDP resistance in OC and should be included in the novel approach to DDP-resistant OC patients.

3.13. Hsa_circ_0000585

Autophagy is an evolved mechanism for intracellular self-digestion that sustains homeostasis under both normal and stressed states. Autophagy is crucial in the pathophysiology of numerous disorders, including those related to aging, autoimmune disorders, cardiovascular diseases, and malignancies. It has been believed that autophagy protectively regulates cisplatin chemosensitivity. SiRNA targeting Beclin1 and autophagy inhibitors increased cisplatin-induced apoptosis, but autophagy activation accounted for most of the cisplatin resistance observed in human OC [192,193]. Although chemotherapy resistance still occurs, paclitaxel is recognized as a first-line treatment for OC [194]. According to Zhang et al., autophagy promotes paclitaxel resistance in OC. In OC, thioredoxin domain containing 17 (TXNDC17) enhanced autophagy upregulation, which in turn boosted paclitaxel resistance [195]. On the other hand, Khurana et al. demonstrated that OC cell lines resistant to chemotherapy had elevated levels of p62 in comparison to those that were sensitive to the drug, indicating a potential down-regulation of autophagy in the former group [196]. It has been seen that has_circ_0000585 increased in SKOV3 cell line resistant to cisplatin in compare with sensitive cell lines. In other words, Overexpression of has_circ_0000585 could attenuate the anti-tumor effect of cisplatin on ovarian cancer cells. P. Du et al. found out that has_circ_0000585 knockdown enhanced the sensitivity of the ovarian cancer cells to cisplatin by inhibiting cellular autophagy which significantly promoted cell death and decreasing cellular cisplatin resistance [197]. Autophagy is a necessary cellular process for the physiological cellular turnover. Thereby, dysregulation in this process is one of the main cause of the tumorgenesis, progression of multiple malignancies and resistance to cisplatin treatment including ovarian cancer [198–200].

4. Conclusion

Recently, circRNAs have been shown to control DDP, docetaxel, and paclitaxel in OC. There has been a lot of interest in circRNA research in DDP resistance, particularly in terms of the competing endogenous RNA (ceRNA) network, which is a useful structure for investigating the pathways driving DDP resistance, such as cancer cell growth and migration. It is intriguing to investigate whether resistance to other chemotherapeutic drugs, including gemcitabine, oxaliplatin, and carboplatin, is affected by circRNAs in OC. It is unclear if circRNAs modulate chemoresistance by interacting with other drug sensitivity variables. Furthermore, it is uncertain if circRNAs and medication resistance in OC are regulated in a feedback loop. Despite the fact that the precise mechanisms are unknown, the significance of circRNAs will be discovered as new resistance mechanisms. Although a few circRNAs enhance DDP sensitivity in OC, most of them enhance DDP resistance. A number of aspects must be addressed to properly comprehend the process of treatment resistance in OC. In addition to circRNAs, miRNAs play important roles in modulating drug resistance in OC through the complex regulatory network of circRNAs/miRNAs/target mRNAs. CSCs are important in the development of treatment resistance. It is necessary to investigate whether circRNAs affect resistance to treatment by targeting ovarian CSC. However, studies are currently focused on preclinical studies, requiring ongoing patient monitoring and evaluation to determine an association between circRNAs and drug resistance. Beyond the few well-defined drugs in OC, identifying more drug resistance-related circRNAs is critical. Additional research into the role of molecular mechanisms of circRNAs in drug resistance and clinical applications will lead to new approaches to OC treatment. Finally, circRNAs appear to be promising targets for chemoresistance prevention and treatment efficacy.

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Abbreviations

OC	Ovarian cancer
ncRNAs	non-coding RNAs
CircRNAs	Circular RNAs
MiRNAs	MicroRNAs
DDP	cisplatin
TME	tumor microenvironment
EMT	Epithelial to mesenchymal transition
CTR	Copper transporters
DDR	DNA damage repair
RBPs	RNA-binding proteins

References

[1] Z. Momenimovahed, A. Tiznobaik, S. Taheri, H. Salehiniya, Ovarian cancer in the world: epidemiology and risk factors, Int. J. Wom. Health (2019) 287–299.
[2] P.A.T.E. Board, Ovarian epithelial, fallopian tube, and primary peritoneal cancer treatment (PDQ®), in: PDQ Cancer Information Summaries, National Cancer Institute (US), 2022 [Internet].
[3] P.C.G.E. Board, BRCA1 and BRCA2: cancer risks and management (PDQ®), in: PDQ Cancer Information Summaries, National Cancer Institute (US), 2023 [Internet].
[4] P.T. Kroeger Jr., R. Drapkin, Pathogenesis and heterogeneity of ovarian cancer, Curr. Opin. Obstet. Gynecol. 29 (1) (2017) 26–34.

[5] S. Lheureux, C. Gourley, I. Vergote, A.M. Oza, Epithelial ovarian cancer, Lancet 393 (10177) (2019) 1240–1253.
[6] L.A. Torre, B. Trabert, C.E. DeSantis, K.D. Miller, G. Samimi, C.D. Runowicz, et al., Ovarian cancer statistics, 2018, CA A Cancer J. Clin. 68 (4) (2018) 284–296.
[7] C. Stewart, C. Ralyea, S. Lockwood (Eds.), Ovarian Cancer: an Integrated Review. Seminars in Oncology Nursing, Elsevier, 2019.
[8] A. Chandra, C. Pius, M. Nabeel, M. Nair, J.K. Vishwanatha, S. Ahmad, et al., Ovarian cancer: current status and strategies for improving therapeutic outcomes, Cancer Med. 8 (16) (2019) 7018–7031.
[9] C. Rooth, Ovarian cancer: risk factors, treatment and management, Br. J. Nurs. 22 (17) (2013) S23–S30.
[10] A. Elies, S. Rivière, N. Pouget, V. Becette, C. Dubot, A. Donnadieu, et al., The role of neoadjuvant chemotherapy in ovarian cancer, Expert Rev. Anticancer Ther. 18 (6) (2018) 555–566.
[11] B. Orr, R.P. Edwards, Diagnosis and treatment of ovarian cancer, Hematol. Oncol. Clin. N. Am. 32 (6) (2018) 943–964.
[12] T.H. Dellinger, E.S. Han, State of the Science: the role of HIPEC in the treatment of ovarian cancer, Gynecol. Oncol. 160 (2) (2021) 364–368.
[13] C.E. Haunschild, K.S. Tewari, Bevacizumab use in the frontline, maintenance and recurrent settings for ovarian cancer, Future Oncol. 16 (7) (2020) 225–246.
[14] M.K. Parmar, J.A. Ledermann, N. Colombo, A. du Bois, J.F. Delaloye, G. B. Kristensen, et al., Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial, Lancet 361 (9375) (2003) 2099–2106.
[15] S. Ghosh, Cisplatin: the first metal based anticancer drug, Bioorg. Chem. 88 (2019) 102925.
[16] S. Dasari, P. Bernard Tchounwou, Cisplatin in cancer therapy: molecular mechanisms of action, Eur. J. Pharmacol. 740 (2014) 364–378.
[17] X. Long, K. Song, H. Hu, Q. Tian, W. Wang, Q. Dong, et al., Long non-coding RNA GAS5 inhibits DDP-resistance and tumor progression of epithelial ovarian cancer via GAS5-E2F4-PARP1-MAPK axis, J. Exp. Clin. Cancer Res. 38 (2019) 1–16.
[18] T. Kimura, Non-coding natural antisense RNA: mechanisms of action in the regulation of target gene expression and its clinical implications, Yakugaku Zasshi: J. Pharm. Soc. Jpn. 140 (5) (2020) 687–700.
[19] A. Zoń, I. Bednarek, Cisplatin in ovarian cancer treatment—known limitations in therapy force new solutions, Int. J. Mol. Sci. 24 (8) (2023) 7585.
[20] M.A. Glasgow, P. Argenta, J.E. Abrahante, M. Shetty, S. Talukdar, P. A. Croonquist, et al., Biological insights into chemotherapy resistance in ovarian cancer, Int. J. Mol. Sci. 20 (9) (2019) 2131.
[21] E. Emmings, S. Mullany, Z. Chang, Jr CN. Landen, S. Linder, M. Bazzaro, Targeting mitochondria for treatment of chemoresistant ovarian cancer, Int. J. Mol. Sci. 20 (1) (2019) 229.
[22] I. Tsibulak, A.G. Zeimet, C. Marth, Hopes and failures in front-line ovarian cancer therapy, Crit. Rev. Oncol.-Hematol. 143 (2019) 14–19.
[23] S. Banerjee, S.B. Kaye, New strategies in the treatment of ovarian cancer: current clinical perspectives and future potential, Clin. Cancer Res. 19 (5) (2013) 961–968.
[24] L. Amable, Cisplatin resistance and opportunities for precision medicine, Pharmacol. Res. 106 (2016) 27–36.
[25] J. Xu, D.A. Gewirtz, Is autophagy always a barrier to cisplatin therapy? Biomolecules 12 (3) (2022).
[26] Y.G. Assaraf, A. Brozovic, A.C. Gonçalves, D. Jurkovicova, A. Linē, M. Machuqueiro, et al., The multi-factorial nature of clinical multidrug resistance in cancer, Drug Resist. Updates 46 (2019) 100645.
[27] S.N. Aleksakhina, A. Kashyap, E.N. Imyanitov, Mechanisms of acquired tumor drug resistance, Biochim. Biophys. Acta Rev. Canc 1872 (2) (2019) 188310.
[28] B. Mansoori, A. Mohammadi, S. Davudian, S. Shirjang, B. Baradaran, The different mechanisms of cancer drug resistance: a brief review, Adv. Pharmaceut. Bull. 7 (3) (2017) 339.
[29] A.J. Sabnis, T.G. Bivona, Principles of resistance to targeted cancer therapy: lessons from basic and translational cancer biology, Trends Mol. Med. 25 (3) (2019) 185–197.
[30] M. Song, M. Cui, K. Liu, Therapeutic strategies to overcome cisplatin resistance in ovarian cancer, Eur. J. Med. Chem. 232 (2022) 114205.
[31] Y.Y. Lee, C.H. Choi, I.G. Do, S.Y. Song, W. Lee, H.S. Park, et al., Prognostic value of the copper transporters, CTR1 and CTR2, in patients with ovarian carcinoma receiving platinum-based chemotherapy, Gynecol. Oncol. 122 (2) (2011) 361–365.
[32] G. Samimi, R. Safaei, K. Katano, A.K. Holzer, M. Rochdi, M. Tomioka, et al., Increased expression of the copper efflux transporter ATP7A mediates resistance to cisplatin, carboplatin, and oxaliplatin in ovarian cancer cells, Clin. Cancer Res. 10 (14) (2004) 4661–4669.
[33] G. Tapia Rico, I. Diaz-Padilla, Molecular mechanisms of platinum resistance in ovarian, Cancer (2013) 205–223.
[34] P. Borkar, P. Bhandari, S. Yadav, A. Prabhu, Cisplatin resistance in ovarian cancer: classical outlook and newer perspectives, Biomedical and Pharmacology Journal 14 (4) (2021) 1993–2005.
[35] C.R.R. Rocha, M.M. Silva, A. Quinet, J.B. Cabral-Neto, C.F.M. Menck, DNA repair pathways and cisplatin resistance: an intimate relationship, Clinics 73 (2018) e478s.
[36] B. Köberle, M.T. Tomicic, S. Usanova, B. Kaina, Cisplatin resistance: preclinical findings and clinical implications, Biochim. Biophys. Acta Rev. Canc 1806 (2) (2010) 172–182.
[37] S.H. Chen, J.Y. Chang, New insights into mechanisms of cisplatin resistance: from tumor cell to microenvironment, Int. J. Mol. Sci. 20 (17) (2019).
[38] Y. Wang, Z. Huang, B. Li, L. Liu, C. Huang, The emerging roles and therapeutic implications of epigenetic modifications in ovarian cancer, Front. Endocrinol. 13 (2022) 863541.
[39] S. Tau, T.W. Miller, The role of cancer cell bioenergetics in dormancy and drug resistance, Cancer Metastasis Rev. 42 (1) (2023) 87–98.
[40] Y. Cen, L. Chen, Z. Liu, Q. Lin, X. Fang, H. Yao, et al., Novel roles of RNA-binding proteins in drug resistance of breast cancer: from molecular biology to targeting therapeutics, Cell Death Discovery 9 (1) (2023) 52.
[41] B. Parma, H. Wurdak, P. Ceppi, Harnessing mitochondrial metabolism and drug resistance in non-small cell lung cancer and beyond by blocking heat-shock proteins, Drug Resist. Updates (2022) 100888.
[42] X. Wang, W. Jiang, Y. Du, D. Zhu, J. Zhang, C. Fang, et al., Targeting feedback activation of signaling transduction pathways to overcome drug resistance in cancer, Drug Resist. Updates (2022) 100884.
[43] P.D. Vos, P.J. Leedman, A. Filipovska, O. Rackham, Modulation of miRNA function by natural and synthetic RNA-binding proteins in cancer, Cell. Mol. Life Sci. 76 (19) (2019) 3745–3752.
[44] S. Lu, T. Wang, G. Zhang, Q.-Y. He, Understanding the proteome encoded by "non-coding RNAs": new insights into human genome, Sci. China Life Sci. 63 (2020) 986–995.
[45] Z. Li, Y. Ruan, H. Zhang, Y. Shen, T. Li, B. Xiao, Tumor-suppressive circular RNAs: mechanisms underlying their suppression of tumor occurrence and use as therapeutic targets, Cancer Sci. 110 (12) (2019) 3630–3638.
[46] A. Huang, H. Zheng, Z. Wu, M. Chen, Y. Huang, Circular RNA-protein interactions: functions, mechanisms, and identification, Theranostics 10 (8) (2020) 3503.
[47] S. Mazloomi, V. Mousavi, E. Aghadavod, A. Mafi, Circular RNAs: emerging modulators in the pathophysiology of polycystic ovary syndrome and their clinical implications, Curr. Mol. Med. 24 (2) (2024) 153–166.
[48] L. Chen, C. Huang, G. Shan, Circular RNAs in physiology and non-immunological diseases, Trends Biochem. Sci. 47 (3) (2022) 250–264.
[49] H. Zhang, Y. Shen, Z. Li, Y. Ruan, T. Li, B. Xiao, et al., The biogenesis and biological functions of circular RNAs and their molecular diagnostic values in cancers, J. Clin. Lab. Anal. 34 (1) (2020) e23049.
[50] C.X. Liu, L.L. Chen, Circular RNAs: characterization, cellular roles, and applications, Cell. 185 (12) (2022) 2016–2034.
[51] J. You, Y. Han, H. Qiao, Y. Han, X. Lu, Y. Lu, et al., Hsa_circ_0063804 enhances ovarian cancer cells proliferation and resistance to cisplatin by targeting miR-1276/CLU axis, Aging (Albany NY) 14 (11) (2022) 4699.
[52] L. Chen, C. Huang, X. Wang, G. Shan, Circular RNAs in eukaryotic cells, Curr. Genom. 16 (5) (2015) 312–318.
[53] S. Memczak, M. Jens, A. Elefsinioti, F. Torti, J. Krueger, A. Rybak, et al., Circular RNAs are a large class of animal RNAs with regulatory potency, Nature 495 (7441) (2013) 333–338.
[54] L. Chen, Y. Wang, J. Lin, Z. Song, Q. Wang, W. Zhao, et al., Exportin 4 depletion leads to nuclear accumulation of a subset of circular RNAs, Nat. Commun. 13 (1) (2022) 5769.
[55] R. Ashwal-Fluss, M. Meyer, N.R. Pamudurti, A. Ivanov, O. Bartok, M. Hanan, et al., circRNA biogenesis competes with pre-mRNA splicing, Mol. Cell 56 (1) (2014) 55–66.
[56] S.J. Conn, K.A. Pillman, J. Toubia, V.M. Conn, M. Salmanidis, C.A. Phillips, et al., The RNA binding protein quaking regulates formation of circRNAs, Cell 160 (6) (2015) 1125–1134.
[57] X. Li, C.-X. Liu, W. Xue, Y. Zhang, S. Jiang, Q.-F. Yin, et al., Coordinated circRNA biogenesis and function with NF90/NF110 in viral infection, Mol. Cell 67 (2) (2017) 214–227. e7.
[58] T. Aktaş, İ. Avşar Ilık, D. Maticzka, V. Bhardwaj, C. Pessoa Rodrigues, G. Mittler, et al., DHX9 suppresses RNA processing defects originating from the Alu invasion of the human genome, Nature 544 (7648) (2017) 115–119.
[59] G. Di Timoteo, D. Dattilo, A. Centron-Broco, A. Colantoni, M. Guarnacci, F. Rossi, et al., Modulation of circRNA metabolism by m6A modification, Cell Rep. 31 (6) (2020).
[60] C. Tang, Y. Xie, T. Yu, N. Liu, Z. Wang, R.J. Woolsey, et al., m6A-dependent biogenesis of circular RNAs in male germ cells, Cell Res. 30 (3) (2020) 211–228.
[61] C.X. Liu, X. Li, F. Nan, S. Jiang, X. Gao, S.K. Guo, et al., Structure and degradation of circular RNAs regulate PKR activation in innate immunity, Cell 177 (4) (2019), 865-80.e21.
[62] O.H. Park, H. Ha, Y. Lee, S.H. Boo, D.H. Kwon, H.K. Song, et al., Endoribonucleolytic cleavage of m(6)a-containing RNAs by RNase P/MRP complex, Mol. Cell. 74 (3) (2019) 494–507.e8.
[63] J.W. Fischer, V.F. Busa, Y. Shao, A.K.L. Leung, Structure-Mediated RNA decay by UPF1 and G3BP1, Mol. Cell. 78 (1) (2020) 70–84.e6.
[64] T.B. Hansen, E.D. Wiklund, J.B. Bramsen, S.B. Villadsen, A.L. Statham, S.J. Clark, et al., miRNA-dependent gene silencing involving Ago2-mediated cleavage of a circular antisense RNA, EMBO J. 30 (21) (2011) 4414–4422.
[65] R. Jia, M.S. Xiao, Z. Li, G. Shan, C. Huang, Defining an evolutionarily conserved role of GW182 in circular RNA degradation, Cell Discov 5 (2019) 45.
[66] M. Hanan, H. Soreq, S. Kadener, CircRNAs in the brain, RNA Biol. 14 (8) (2017) 1028–1034.
[67] O. Vakili, P. Asili, Z. Babaei, M. Mirahmad, A. Keshavarzmotamed, Z. Asemi, et al., Circular RNAs in alzheimer's disease: a new perspective of diagnostic and therapeutic targets, CNS Neurol. Disord. Drug Targets. 22 (9) (2022) 1335–1354.
[68] Y. Zhang, X.O. Zhang, T. Chen, J.F. Xiang, Q.F. Yin, Y.H. Xing, et al., Circular intronic long noncoding RNAs, Mol Cell. 51 (6) (2013) 792–806.

[69] Z. Li, C. Huang, C. Bao, L. Chen, M. Lin, X. Wang, et al., Exon-intron circular RNAs regulate transcription in the nucleus, Nat. Struct. Mol. Biol. 22 (3) (2015) 256–264.
[70] Q. Yang, W.W. Du, N. Wu, W. Yang, F.M. Awan, L. Fang, et al., A circular RNA promotes tumorigenesis by inducing c-myc nuclear translocation, Cell Death Differ. 24 (9) (2017) 1609–1620.
[71] L. Wang, H. Long, Q. Zheng, X. Bo, X. Xiao, B. Li, Circular RNA circRHOT1 promotes hepatocellular carcinoma progression by initiation of NR2F6 expression, Mol. Cancer 18 (1) (2019) 119.
[72] C. Huang, D. Liang, D.C. Tatomer, J.E. Wilusz, A length-dependent evolutionarily conserved pathway controls nuclear export of circular RNAs, Genes Dev. 32 (9–10) (2018) 639–644.
[73] R.X. Chen, X. Chen, L.P. Xia, J.X. Zhang, Z.Z. Pan, X.D. Ma, et al., N(6)-methyladenosine modification of circNSUN2 facilitates cytoplasmic export and stabilizes HMGA2 to promote colorectal liver metastasis, Nat. Commun. 10 (1) (2019) 4695.
[74] M. Wang, F. Yu, P. Li, K. Wang, Emerging function and clinical significance of exosomal circRNAs in cancer, Mol. Ther. Nucleic Acids 21 (2020) 367–383.
[75] Q. Yi, J. Yue, Y. Liu, H. Shi, W. Sun, J. Feng, et al., Recent advances of exosomal circRNAs in cancer and their potential clinical applications, J. Transl. Med. 21 (1) (2023) 516.
[76] Y. Li, Q. Zheng, C. Bao, S. Li, W. Guo, J. Zhao, et al., Circular RNA is enriched and stable in exosomes: a promising biomarker for cancer diagnosis, Cell Res. 25 (8) (2015) 981–984.
[77] B. Ren, M.X. Guan, T. Zhou, X. Cai, G. Shan, Emerging functions of mitochondria-encoded noncoding RNAs, Trends Genet. 39 (2) (2023) 125–139.
[78] X. Liu, X. Wang, J. Li, S. Hu, Y. Deng, H. Yin, et al., Identification of mecciRNAs and their roles in the mitochondrial entry of proteins, Sci. China Life Sci. 63 (10) (2020) 1429–1449.
[79] Q. Zhao, J. Liu, H. Deng, R. Ma, J.Y. Liao, H. Liang, et al., Targeting mitochondria-located circRNA SCAR alleviates NASH via reducing mROS output, Cell 183 (1) (2020) 76–93.e22.
[80] X. Liu, X. Wang, J. Li, S. Hu, Y. Deng, H. Yin, et al., Identification of mecciRNAs and their roles in the mitochondrial entry of proteins, Sci. China Life Sci. 63 (2020) 1429–1449.
[81] Y. Enuka, M. Lauriola, M.E. Feldman, A. Sas-Chen, I. Ulitsky, Y. Yarden, Circular RNAs are long-lived and display only minimal early alterations in response to a growth factor, Nucleic Acids Res. 44 (3) (2016) 1370–1383.
[82] W.W. Du, W. Yang, E. Liu, Z. Yang, P. Dhaliwal, B.B. Yang, Foxo3 circular RNA retards cell cycle progression via forming ternary complexes with p21 and CDK2, Nucleic Acids Res. 44 (6) (2016) 2846–2858.
[83] A. Sudheesh, N. Mohan, N. Francis, R.S. Laishram, R.A. Anderson, Star-PAP controlled alternative polyadenylation coupled poly (A) tail length regulates protein expression in hypertrophic heart, Nucleic Acids Res. 47 (20) (2019) 10771–10787.
[84] W.R. Jeck, J.A. Sorrentino, K. Wang, M.K. Slevin, C.E. Burd, J. Liu, et al., Circular RNAs are abundant, conserved, and associated with ALU repeats, RNA 19 (2) (2013) 141–157.
[85] K. Sun, H. Yao, P. Zhang, Y. Sun, J. Ma, Q. Xia, Emerging landscape of circFNDC3B and its role in human malignancies, Front. Oncol. 13 (2023) 99.
[86] L. Chen, G. Shan, CircRNA in cancer: fundamental mechanism and clinical potential, Cancer Lett. 505 (2021) 49–57.
[87] T. Yu, Y. Wang, Y. Fan, N. Fang, T. Wang, T. Xu, et al., CircRNAs in cancer metabolism: a review, J. Hematol. Oncol. 12 (2019) 1–10.
[88] M. Su, Y. Xiao, J. Ma, Y. Tang, B. Tian, Y. Zhang, et al., Circular RNAs in Cancer: emerging functions in hallmarks, stemness, resistance and roles as potential biomarkers, Mol. Cancer 18 (1) (2019) 1–17.
[89] Y. Zheng, Z. Li, Y. Wang, W. Chen, Y. Lin, J. Guo, et al., CircRNA: a new class of targets for gastric cancer drug resistance therapy, Pathol. Oncol. Res. 29 (2023) 1611033.
[90] Y. Zhang, J. Luo, W. Yang, W.-C. Ye, CircRNAs in colorectal cancer: potential biomarkers and therapeutic targets, Cell Death Dis. 14 (6) (2023) 353.
[91] A. Mafi, H. Rismanchi, M. Malek Mohammadi, N. Hedayati, S.S. Ghorbanhosseini, S.A. Hosseini, et al., A spotlight on the interplay between Wnt/β-catenin signaling and circular RNAs in hepatocellular carcinoma progression, Front. Oncol. 13 (2023) 1224138.
[92] Q. Chen, J. Li, P. Shen, H. Yuan, J. Yin, W. Ge, et al., Biological functions, mechanisms, and clinical significance of circular RNA in pancreatic cancer: a promising rising star, Cell Biosci. 12 (1) (2022) 97.
[93] W.R. Kim, E.G. Park, D.H. Lee, Y.J. Lee, W.H. Bae, H.-S. Kim, The tumorigenic role of circular RNA-MicroRNA Axis in cancer, Int. J. Mol. Sci. 24 (3) (2023) 3050.
[94] S. D'ambrosi, A. Visser, M. Antunes-Ferreira, A. Poutsma, S. Giannoukakos, N. Sol, et al., The analysis of platelet-derived circRNA repertoire as potential diagnostic biomarker for non-small cell lung cancer, Cancers 13 (18) (2021) 4644.
[95] Y. Sang, B. Chen, X. Song, Y. Li, Y. Liang, D. Han, et al., circRNA_0025202 regulates tamoxifen sensitivity and tumor progression via regulating the miR-182-5p/FOXO3a axis in breast cancer, Mol. Ther. 27 (9) (2019) 1638–1652.
[96] J. Shang, W.-M. Chen, Z.-H. Wang, T.-N. Wei, Z.-Z. Chen, W.-B. Wu, CircPAN3 mediates drug resistance in acute myeloid leukemia through the miR-153-5p/miR-183-5p–XIAP axis, Exp. Hematol. 70 (2019) 42–54. e3.
[97] Y. Zhao, Y. Hu, Q. Shen, Q. Chen, X.-J. Zhu, S.-S. Jiang, et al., CircRNA_MYLK promotes malignant progression of ovarian cancer through regulating microRNA-652, Eur. Rev. Med. Pharmacol. Sci. 24 (10) (2020).
[98] X. Li, S. Lin, Z. Mo, J. Jiang, H. Tang, C. Wu, et al., CircRNA_100395 inhibits cell proliferation and metastasis in ovarian cancer via regulating miR-1228/p53/epithelial-mesenchymal transition (EMT) axis, J. Cancer 11 (3) (2020) 599.
[99] S. Chen, W. Wu, Q-h Li, B-m Xie, F. Shen, Y-p Du, et al., Circ-NOLC1 promotes epithelial ovarian cancer tumorigenesis and progression by binding ESRP1 and modulating CDK1 and RhoA expression, Cell death discovery 7 (1) (2021) 22.
[100] Y. Luo, R. Gui, Circulating exosomal circFoxp1 confers cisplatin resistance in epithelial ovarian cancer cells, Journal of gynecologic oncology 31 (5) (2020).
[101] Z. Zhao, M. Ji, Q. Wang, N. He, Y. Li, Circular RNA Cdr1as upregulates SCAI to suppress cisplatin resistance in ovarian cancer via miR-1270 suppression, Mol. Ther. Nucleic Acids 18 (2019) 24–33.
[102] J. Yin, H.-Y. Huang, Y. Long, Y. Ma, M. Kamalibaike, R. Dawuti, et al., circ_C20orf11 enhances DDP resistance by inhibiting miR-527/YWHAZ through the promotion of extracellular vesicle-mediated macrophage M2 polarization in ovarian cancer, Cancer Biol. Ther. 22 (7–9) (2021) 440–454.
[103] C. Dai, S.Y. Dai, Y. Gao, T. Yan, Q.Y. Zhou, S.J. Liu, et al., Circ_0078607 increases platinum drug sensitivity via miR-196b-5p/GAS7 axis in ovarian cancer, Epigenetics 18 (1) (2023) 2175565.
[104] Z. Foruzandeh, F. Zeinali-Sehrig, K. Nejati, D. Rahmanpour, F. Pashazadeh, F. Seif, et al., CircRNAs as potent biomarkers in ovarian cancer: a systematic scoping review, Cell. Mol. Biol. Lett. 26 (1) (2021) 41.
[105] I.V. Pronina, L.A. Uroshlev, A.A. Moskovtsev, D.M. Zaichenko, E.A. Filippova, M. V. Fridman, et al., Dysregulation of lncRNA–miRNA–mRNA interactome as a marker of metastatic process in ovarian cancer, Biomedicines 10 (4) (2022) 824.
[106] F. Xu, M. Ni, J. Li, J. Cheng, H. Zhao, J. Zhao, et al., Circ0004390 promotes cell proliferation through sponging miR-198 in ovarian cancer, Biochem. Biophys. Res. Commun. 526 (1) (2020) 14–20.
[107] M.T. van Jaarsveld, P.F. van Kuijk, A.W. Boersma, J. Helleman, I.W.F. van, R. H. Mathijssen, et al., miR-634 restores drug sensitivity in resistant ovarian cancer cells by targeting the Ras-MAPK pathway, Mol. Cancer 14 (2015) 196.
[108] X. Liu, Z. Yin, Y. Wu, Q. Zhan, H. Huang, J. Fan, Circular RNA lysophosphatidic acid receptor 3 (circ-LPAR3) enhances the cisplatin resistance of ovarian cancer, Bioengineered 13 (2) (2022) 3739–3750.
[109] Orouei S, Hashemi M, Rahmanian P, Gholami MH, Yang MH, Ahn KS. Circular RNAs (CircRNAs) in cancer therapy response: biological aspects. Non-coding RNA Transcripts in Cancer Therapy. p. 283-317.
[110] M. Qin, C. Zhang, Y. Li, Circular RNAs in gynecologic cancers: mechanisms and implications for chemotherapy resistance, Front. Pharmacol. 14 (2023) 1194719.
[111] J. Halder, D. Pradhan, B. Kar, G. Ghosh, G. Rath, Nanotherapeutics approaches to overcome P-glycoprotein-mediated multi-drug resistance in cancer, Nanomed. Nanotechnol. Biol. Med. 40 (2022) 102494.
[112] A. Martincuks, J. Song, A. Kohut, C. Zhang, Y.-J. Li, Q. Zhao, et al., PARP inhibition activates STAT3 in both tumor and immune cells underlying therapy resistance and immunosuppression in ovarian cancer, Front. Oncol. 11 (2021) 724104.
[113] J. Zhang, Y. Kan, Y. Tian, Z. Wang, J. Zhang, Effects of poly (ADP-ribosyl) polymerase (PARP) inhibitor on cisplatin resistance & proliferation of the ovarian cancer C13* cells, Indian J. Med. Res. 137 (3) (2013) 527.
[114] L. Wu, S. Cai, Y. Deng, Z. Zhang, X. Zhou, Y. Su, et al., PD-1/PD-L1 enhanced cisplatin resistance in gastric cancer through PI3K/AKT mediated P-gp expression, Int. Immunopharm. 94 (2021) 107443.
[115] C. Lu, Z. Shan, C. Li, L. Yang, MiR-129 regulates cisplatin-resistance in human gastric cancer cells by targeting P-gp, Biomed. Pharmacother. 86 (2017) 450–456.
[116] Q. Shi, L. Shen, B. Dong, H. Fu, X. Kang, L. Dai, et al., Downregulation of HOXA13 sensitizes human esophageal squamous cell carcinoma to chemotherapy, Thoracic Cancer 9 (7) (2018) 836–846.
[117] C. He, Z. Sun, R.M. Hoffman, Z. Yang, Y. Jiang, L. Wang, et al., P-glycoprotein overexpression is associated with cisplatin resistance in human osteosarcoma, Anticancer Res. 39 (4) (2019) 1711–1718.
[118] S. Torkashvand, Z. Damavandi, B. Mirzaei, M. Tavallaei, M. Vasei, S.J. Mowla, Decreased expression of bioinformatically predicted piwil2-targetting microRNAs, miR-1267 and miR-2276 in breast cancer, Arch. Iran. Med. 19 (6) (2016) 420–425.
[119] Z. Zhang, H. Zhao, G. Zhou, R. Han, Z. Sun, M. Zhong, et al., Circ_0002623 promotes bladder cancer progression by regulating the miR-1276/SMAD2 axis, Cancer Sci. 113 (4) (2022) 1250–1263.
[120] H. Zhang, H. Huang, X. Xu, H. Wang, J. Wang, Z. Yao, et al., LncRNA HCG11 promotes proliferation and migration in gastric cancer via targeting miR-1276/CTNNB1 and activating Wnt signaling pathway, Cancer Cell Int. 19 (1) (2019) 1–12.
[121] Y. Fu, Y. Lai, Q. Wang, X. Liu, W. He, H. Zhang, et al., Overexpression of clusterin promotes angiogenesis via the vascular endothelial growth factor in primary ovarian cancer, Mol. Med. Rep. 7 (6) (2013) 1726–1732.
[122] M.K. Hassan, H. Watari, Y. Han, T. Mitamura, M. Hosaka, L. Wang, et al., Clusterin is a potential molecular predictor for ovarian cancer patient's survival: targeting clusterin improves response to paclitaxel, J. Exp. Clin. Cancer Res. 30 (1) (2011) 1–15.
[123] B. Zhang, Z-m Liu, F-g Hao, M. Wang, siRNA-directed clusterin silencing promotes cisplatin antitumor activity in human non-small cell lung cancer xenografts in immunodeficient mice, Eur. Rev. Med. Pharmacol. Sci. 18 (2014).
[124] H. Miyake, I. Hara, S. Kamidono, M.E. Gleave, Synergistic chemsensitization and inhibition of tumor growth and metastasis by the antisense oligodeoxynucleotide targeting clusterin gene in a human bladder cancer model, Clin. Cancer Res. 7 (12) (2001) 4245–4252.

[125] Q. Lu, X. Yang, W. Yuan, R. Zhou, J. Wang, J. Han, et al., MP51-17 circular RNA CDR1AS sensitizes bladder cancer to cisplatin by sponging MIR-1270 and regulating APAF1 expression, J. Urol. 201 (Supplement 4) (2019) e730–e.
[126] Q. Zhong, J. Huang, J. Wei, R. Wu, Circular RNA CDR1as sponges miR-7-5p to enhance E2F3 stability and promote the growth of nasopharyngeal carcinoma, Cancer Cell Int. 19 (1) (2019) 1–13.
[127] L. Meng, S. Liu, P. Ding, S. Chang, M. Sang, Circular RNA ciRS-7 inhibits autophagy of ESCC cells by functioning as miR-1299 sponge to target EGFR signaling, J. Cell. Biochem. 121 (2) (2020) 1039–1049.
[128] H. Wu, X. Zhao, J. Wang, X. Jiang, Y. Cheng, Y. He, et al., Circular RNA CDR1as alleviates cisplatin-based chemoresistance by suppressing MiR-1299 in ovarian cancer, Front. Genet. 12 (2021) 815448.
[129] S.J. Dixon, K.M. Lemberg, M.R. Lamprecht, R. Skouta, E.M. Zaitsev, C.E. Gleason, et al., Ferroptosis: an iron-dependent form of nonapoptotic cell death, cell 149 (5) (2012) 1060–1072.
[130] W.S. Yang, R. SriRamaratnam, M.E. Welsch, K. Shimada, R. Skouta, V. S. Viswanathan, et al., Regulation of ferroptotic cancer cell death by GPX4, Cell. 156 (1) (2014) 317–331.
[131] L. Jiang, N. Kon, T. Li, S.-J. Wang, T. Su, H. Hibshoosh, et al., Ferroptosis as a p53-mediated activity during tumour suppression, Nature 520 (7545) (2015) 57–62.
[132] Y. Wang, Z. Wei, K. Pan, J. Li, Q. Chen, The function and mechanism of ferroptosis in cancer, Apoptosis 25 (11) (2020) 786–798.
[133] B. Lu, X.B. Chen, M.D. Ying, Q.J. He, J. Cao, B. Yang, The role of ferroptosis in cancer development and treatment response, Front. Pharmacol. 8 (2018) 992.
[134] K. Hadian, B.R. Stockwell, A roadmap to creating ferroptosis-based medicines, Nat. Chem. Biol. 17 (11) (2021) 1113–1116.
[135] H.-H. Zhou, X. Chen, L.-Y. Cai, X.-W. Nan, J.-H. Chen, X.-X. Chen, et al., Erastin reverses ABCB1-mediated docetaxel resistance in ovarian cancer, Front. Oncol. 9 (2019) 1398.
[136] X. Chen, J. Li, R. Kang, D.J. Klionsky, D. Tang, Ferroptosis: machinery and regulation, Autophagy 17 (9) (2021) 2054–2081.
[137] T. Hong, G. Lei, X. Chen, H. Li, X. Zhang, N. Wu, et al., PARP inhibition promotes ferroptosis via repressing SLC7A11 and synergizes with ferroptosis inducers in BRCA-proficient ovarian cancer, Redox Biol. 42 (2021) 101928.
[138] K. Qin, F. Zhang, H. Wang, N. Wang, H. Qiu, X. Jia, et al., circRNA circSnx12 confers Cisplatin chemoresistance to ovarian cancer by inhibiting ferroptosis through a miR-194-5p/SLC7A11 axis, BMB Rep 56 (2) (2023) 184–189.
[139] H. Zhai, X. Zhang, S. Chen, M. Fan, S. Ma, X. Sun, RP5-1120P11. 3 promotes hepatocellular carcinoma development via the miR-196b-5p–WIPF2 axis, Biochem. Cell. Biol. 98 (2) (2020) 238–248.
[140] W. Liu, F. Cheng, Circular RNA circCRKL inhibits the proliferation of acute myeloid leukemia cells via the miR-196a-5p/miR-196b-5p/p27 axis, Bioengineered 12 (1) (2021) 7704–7713.
[141] G. Liang, W. Meng, X. Huang, W. Zhu, C. Yin, C. Wang, et al., miR-196b-5p–mediated downregulation of TSPAN12 and GATA6 promotes tumor progression in non-small cell lung cancer, Proc. Natl. Acad. Sci. USA 117 (8) (2020) 4347–4357.
[142] H. Xin, C. Wang, Y. Chi, Z. Liu, MicroRNA-196b-5p promotes malignant progression of colorectal cancer by targeting ING5, Cancer Cell Int. 20 (2020) 1–17.
[143] C. Zhou, R. Li, W. Mi, circ_0067934: a potential biomarker and therapeutic target for hepatocellular carcinoma, Ann. Clin. Lab. Sci. 50 (6) (2020) 734–738.
[144] Q. Liu, Q. Zhou, P. Zhong, circ_0067934 increases bladder cancer cell proliferation, migration and invasion through suppressing miR-1304 expression and increasing Myc expression levels, Exp. Ther. Med. 19 (6) (2020) 3751–3759.
[145] Y. Yin, J. Li, J. Rong, B. Zhang, X. Wang, H. Han, Circ_0067934 reduces JNK phosphorylation through a microRNA-545-3p/PPA1 axis to enhance tumorigenesis and cisplatin resistance in ovarian cancer, Immunopharmacol. Immunotoxicol. 44 (2) (2022) 261–274.
[146] C. Hu, Y. Wang, A. Li, J. Zhang, F. Xue, L. Zhu, Overexpressed circ_0067934 acts as an oncogene to facilitate cervical cancer progression via the miR-545/EIF3C axis, J. Cell. Physiol. 234 (6) (2019) 9225–9232.
[147] J. Wang, X. Li, J. Wang, Circular RNA circ_0067934 functions as an oncogene in breast cancer by targeting Mcl-1, Eur. Rev. Med. Pharmacol. Sci. 24 (13) (2020) 7214.
[148] S. Wang, J. Wei, S. Li, Y. Luo, Y. Li, X. Wang, et al., PPA1, an energy metabolism initiator, plays an important role in the progression of malignant tumors, Front. Oncol. 12 (2022) 1012090.
[149] D. Luo, D. Liu, W. Shi, H. Jiang, W. Liu, X. Zhang, et al., PPA1 promotes NSCLC progression via a JNK-and TP53-dependent manner, Oncogenesis 8 (10) (2019) 53.
[150] S. Zhao, S. Fan, Y. Shi, H. Ren, H. Hong, X. Gao, et al., Propranolol induced apoptosis and autophagy via the ROS/JNK signaling pathway in Human Ovarian Cancer, J. Cancer 11 (20) (2020) 5900.
[151] Q. Wu, W. Wu, B. Fu, L. Shi, X. Wang, K. Kuca, JNK signaling in cancer cell survival, Med. Res. Rev. 39 (6) (2019) 2082–2104.
[152] R. Kalluri, V.S. LeBleu, The biology, function, and biomedical applications of exosomes, Science 367 (6478) (2020) eaau6977.
[153] L. Huang, X. Tang, X. Shi, L. Su, miR-532-5p promotes breast cancer proliferation and migration by targeting RERG, Exp. Ther. Med. 19 (1) (2020) 400–408.
[154] Y. Wang, J. Liu, D. Liu, X. Wang, A. Bian, D. Fang, et al., MiR-532-5p acts as a tumor suppressor and inhibits glioma cell proliferation by targeting CSF1, Eur. Rev. Med. Pharmacol. Sci. 24 (13) (2020) 7206.
[155] J. Hu, L. Wang, C. Guan, MiR-532-5p suppresses migration and invasion of lung cancer cells through inhibiting CCR4, Cancer Biother. Radiopharm. 35 (9) (2020) 673–681.
[156] H. Wei, Q. Tang, K. Zhang, J. Sun, R. Ding, miR-532-5p is a prognostic marker and suppresses cells proliferation and invasion by targeting TWIST1 in epithelial ovarian cancer, Eur. Rev. Med. Pharmacol. Sci. 22 (18) (2018).
[157] K. Huang, D. Liu, C. Su, Circ_0007841 accelerates ovarian cancer development through facilitating MEX3C expression by restraining miR-151-3p activity, Aging (albany NY) 13 (8) (2021) 12058.
[158] Y. Gao, Y. Huang, Circ_0007841 knockdown confers cisplatin sensitivity to ovarian cancer cells by down-regulation of NFIB expression in a miR-532-5p-dependent manner, J. Chemother. 35 (2) (2023) 117–130.
[159] N. Wang, J. Yuan, F. Liu, J. Wei, Y. Liu, M. Xue, et al., NFIB promotes the migration and progression of kidney renal clear cell carcinoma by regulating PINK1 transcription, PeerJ 9 (2021) e10848.
[160] T. Chen, X. Wang, C. Li, H. Zhang, Y. Liu, D. Han, et al., CircHIF1A regulated by FUS accelerates triple-negative breast cancer progression by modulating NFIB expression and translocation, Oncogene 40 (15) (2021) 2756–2771.
[161] D. Li, G. Wang, G. Jin, K. Yao, Z. Zhao, L. Bie, et al., Resveratrol suppresses colon cancer growth by targeting the AKT/STAT3 signaling pathway, Int. J. Mol. Med. 43 (1) (2019) 630–640.
[162] W. Zhang, X. Su, S. Li, Z. Liu, Q. Wang, H. Zeng, Low serum exosomal miR-484 expression predicts unfavorable prognosis in ovarian cancer, Cancer Biomarkers 27 (4) (2020) 485–491.
[163] Y. Huang, L. Lin, Z. Shen, Y. Li, H. Cao, L. Peng, et al., CEBPG promotes esophageal squamous cell carcinoma progression by enhancing PI3K-AKT signaling, Am. J. Cancer Res. 10 (10) (2020) 3328.
[164] S.H. Mueller, A.G. Lai, M. Valkovskaya, K. Michailidou, M.K. Bolla, Q. Wang, et al., Aggregation tests identify new gene associations with breast cancer in populations with diverse ancestry, Genome Med. 15 (1) (2023) 1–18.
[165] J. Liu, S. Chen, Y. Chen, N. Geng, C. Feng, High expression of FMNL3 associates with cancer cell migration, invasion, and unfavorable prognosis in tongue squamous cell carcinoma, J. Oral Pathol. Med. 48 (6) (2019) 459–467.
[166] W. Zong, W. Feng, Y. Jiang, Y. Cao, Y. Ke, X. Shi, et al., LncRNA CTC-497E21. 4 promotes the progression of gastric cancer via modulating miR-22/NET1 axis through RhoA signaling pathway, Gastric Cancer 23 (2020) 228–240.
[167] K. Wu, T. Xu, X. Song, J. Shen, S. Zheng, L. Zhang, et al., LncRNA SLCO4A1-AS1 modulates colon cancer stem cell properties by binding to miR-150-3p and positively regulating SLCO4A1, Lab. Invest. 101 (7) (2021) 908–920.
[168] Y. Yang, Y. Yang, J. Yang, X. Zhao, X. Wei, Tumor microenvironment in ovarian cancer: function and therapeutic strategy, Front. Cell Dev. Biol. 8 (2020) 758.
[169] Y. Jiang, Y. Wan, M. Gong, S. Zhou, J. Qiu, W. Cheng, RNA demethylase ALKBH5 promotes ovarian carcinogenesis in a simulated tumour microenvironment through stimulating NF-κB pathway, J. Cell Mol. Med. 24 (11) (2020) 6137–6148.
[170] H. Zhao, Y. Teng, W. Hao, J. Li, Z. Li, Q. Chen, et al., Single-cell analysis revealed that IL4I1 promoted ovarian cancer progression, J. Transl. Med. 19 (1) (2021) 1–15.
[171] R. Dietze, M.K. Hammoud, M. Gómez-Serrano, A. Unger, T. Bieringer, F. Finkernagel, et al., Phosphoproteomics identify arachidonic-acid-regulated signal transduction pathways modulating macrophage functions with implications for ovarian cancer, Theranostics 11 (3) (2021) 1377.
[172] M. Song, O.O. Yeku, S. Rafiq, T. Purdon, X. Dong, L. Zhu, et al., Tumor derived UBR5 promotes ovarian cancer growth and metastasis through inducing immunosuppressive macrophages, Nat. Commun. 11 (1) (2020) 6298.
[173] T. Shree, O.C. Olson, B.T. Elie, J.C. Kester, A.L. Garfall, K. Simpson, et al., Macrophages and cathepsin proteases blunt chemotherapeutic response in breast cancer, Gene Dev. 25 (23) (2011) 2465–2479.
[174] Q. Zhang, W. Wang, Q. Zhou, C. Chen, W. Yuan, J. Liu, et al., Roles of circRNAs in the tumour microenvironment, Mol. Cancer 19 (1) (2020) 14.
[175] M.-M. Chang, S.-Z. Wu, S.-H. Yang, C.-C. Wu, C.-Y. Wang, B.-M. Huang, FGF9/FGFR1 promotes cell proliferation, epithelial-mesenchymal transition, M2 macrophage infiltration and liver metastasis of lung cancer, Translational Oncology 14 (11) (2021) 101208.
[176] H. Li, F. Luo, X. Jiang, W. Zhang, T. Xiang, Q. Pan, et al., CircITGB6 promotes ovarian cancer cisplatin resistance by resetting tumor-associated macrophage polarization toward the M2 phenotype, Journal for Immunotherapy of Cancer 10 (3) (2022).
[177] L. Fu, D. Zhang, N. Yi, Y. Cao, Y. Wei, W. Wang, et al., Circular RNA circPBX3 promotes cisplatin resistance of ovarian cancer cells via interacting with IGF2BP2 to stabilize ATP7A mRNA expression, Hum. Cell 35 (5) (2022) 1560–1576.
[178] J. Guo, Y. Sun, G. Liu, The mechanism of copper transporters in ovarian cancer cells and the prospect of cuproptosis, J. Inorg. Biochem. (2023) 112324.
[179] D. Lukanović, M. Herzog, B. Kobal, K. Černe, The contribution of copper efflux transporters ATP7A and ATP7B to chemoresistance and personalized medicine in ovarian cancer, Biomed. Pharmacother. 129 (2020) 110401.
[180] F. Xiao, S. Xiao, M. Xue, miR-139 controls viability of ovarian cancer cells through apoptosis induction and exosome shedding inhibition by targeting ATP7A, OncoTargets Ther. 12 (2019) 10727.
[181] L. Wei, W. He, H. Zhao, P. Zhao, Circ_0026123 promotes cisplatin resistance and progression of ovarian cancer by upregulating RAB1A through sequestering miR-543, Anti Cancer Drugs 33 (10) (2022) 1069–1080.
[182] X. Yang, J. Wang, H. Li, Y. Sun, X. Tong, Downregulation of hsa_circ_0026123 suppresses ovarian cancer cell metastasis and proliferation through the miR-124-3p/EZH2 signaling pathway, Int. J. Mol. Med. 47 (2) (2021) 668–676.
[183] Q. Yu, Z. Zhang, B. He, H. Wang, P. Shi, Y. Li, MiR-543 functions as tumor suppressor in ovarian cancer by targeting TWIST1, J. Biol. Regul. Homeost. Agents 34 (1) (2020) 101–110.

[184] C. Qu, C. Dai, Y. Guo, R. Qin, J. Liu, Long non-coding RNA PVT1-mediated miR-543/SERPINI1 axis plays a key role in the regulatory mechanism of ovarian cancer, Biosci. Rep. 40 (6) (2020) BSR20200800.
[185] Y. Zhang, Q. Di, J. Chen, M. Chang, Y. Ma, J. Yu, Circ_0061140 contributes to the malignant progression in ovarian cancer cells by mediating the RAB1A level through sponging miR-361-5p, Biochem. Genet. 60 (6) (2022) 1946–1962.
[186] X.-Z. Yang, X.-M. Chen, L.-S. Zeng, J. Deng, L. Ma, C. Jin, et al., Rab1A promotes cancer metastasis and radioresistance through activating GSK-3β/Wnt/β-catenin signaling in nasopharyngeal carcinoma, Aging (Albany NY) 12 (20) (2020) 20380.
[187] Q. Zhang, C. Zhang, J.-X. Ma, H. Ren, Y. Sun, J.-Z. Xu, Circular RNA PIP5K1A promotes colon cancer development through inhibiting miR-1273a, World J. Gastroenterol. 25 (35) (2019) 5300.
[188] Y. Ma, X. Cong, Y. Zhang, X. Yin, Z. Zhu, Y. Xue, CircPIP5K1A facilitates gastric cancer progression via miR-376c-3p/ZNF146 axis, Cancer Cell Int. 20 (2020) 1–12.
[189] Z. Sun, J. Han, J. Wang, Circular RNA PIP5K1A promotes glycolysis and malignancy of non-small cell lung cancer via miR-656-3p/GBE1 axis under hypoxia, Molecular & Cellular Toxicology (2023) 1–13.
[190] H. Sheng, X. Wang, Knockdown of circ-PIP5K1A overcomes resistance to cisplatin in ovarian cancer by miR-942-5p/NFIB axis, Anti Cancer Drugs 34 (2) (2023) 214–226.
[191] Z. Du, L. Wang, Y. Xia, Circ_0015756 promotes the progression of ovarian cancer by regulating miR-942-5p/CUL4B pathway, Cancer Cell Int. 20 (1) (2020) 1–13.
[192] Y. Sun, J.H. Liu, L. Jin, Y.X. Sui, L.L. Han, Y. Huang, Effect of autophagy-related beclin1 on sensitivity of cisplatin-resistant ovarian cancer cells to chemotherapeutic agents, Asian Pac. J. Cancer Prev. APJCP 16 (7) (2015) 2785–2791.
[193] L. Bao, M.C. Jaramillo, Z. Zhang, Y. Zheng, M. Yao, D.D. Zhang, et al., Induction of autophagy contributes to cisplatin resistance in human ovarian cancer cells, Mol. Med. Rep. 11 (1) (2015) 91–98.
[194] M. Ortiz, E. Wabel, K. Mitchell, S. Horibata, Mechanisms of chemotherapy resistance in ovarian cancer, Cancer Drug Resist 5 (2) (2022) 304–316.
[195] S.F. Zhang, X.Y. Wang, Z.Q. Fu, Q.H. Peng, J.Y. Zhang, F. Ye, et al., TXNDC17 promotes paclitaxel resistance via inducing autophagy in ovarian cancer, Autophagy 11 (2) (2015) 225–238.
[196] A. Khurana, D. Roy, E. Kalogera, S. Mondal, X. Wen, X. He, et al., Quinacrine promotes autophagic cell death and chemosensitivity in ovarian cancer and attenuates tumor growth, Oncotarget 6 (34) (2015) 36354–36369.
[197] P. Du, X. Xu, Y. Wang, Hsa_circ_0000585 promotes chemoresistance to cis-platin in epithelial cells of ovarian cancer by modulating autophagy, Biochem. Biophys. Res. Commun. 678 (2023) 186–192.
[198] Y. Zhou, T. Liu, Q. Wu, H. Wang, Y. Sun, Baohuoside I inhibits resistance to cisplatin in ovarian cancer cells by suppressing autophagy via downregulating HIF-1α/ATG5 axis, Mol. Carcinog. 62 (10) (2023) 1474–1486.
[199] Y. Meng, L. Qiu, X. Zeng, X. Hu, Y. Zhang, X. Wan, et al., Targeting CRL4 suppresses chemoresistant ovarian cancer growth by inducing mitophagy, Signal Transduct. Targeted Ther. 7 (1) (2022) 388.
[200] P. Xu, S. Xu, H. Pan, C. Dai, Y. Xu, L. Wang, et al., Differential effects of the LncRNA RNF157-AS1 on epithelial ovarian cancer cells through suppression of DIRAS3-and ULK1-mediated autophagy, Cell Death Dis. 14 (2) (2023) 140.
[201] S. Tahmasebi, M. Alimohammadi, S. Khorasani, N. Rezaei, Pro-tumorigenic and Anti-tumorigenic Roles of Pro-inflammatory Cytokines in Cancer, in: N. Rezaei (Ed.), Handbook of Cancer and Immunology, Springer International Publishing, Cham, 2022, pp. 1–25.
[202] M. Alimohammadi, S. Makaremi, A. Rahimi, V. Asghariazar, M. Taghadosi, E. Safarzadeh, DNA methylation changes and inflammaging in aging-associated diseases, Epigenomics 14 (16) (2022) 965–986.
[203] M. Rezaee, F. Mohammadi, A. Keshavarzmotamed, S. Yahyazadeh, O. Vakili, Y. E. Milasi, V. Veisi, R.M. Dehmordi, S. Asadi, S.S. Ghorbanhosseini, M. Rostami, M. Alimohammadi, A. Azadi, N. Moussavi, Z. Asemi, A. Aminianfar, H. Mirzaei, A. Mafi, The landscape of exosomal non-coding RNAs in breast cancer drug resistance, focusing on underlying molecular mechanisms, Front. Pharmacol. 14 (2023) 1152672.