Review | Received 27 September 2024; Accepted 6 December 2024; Published 17 December 2024
https://doi.org/10.55092/exrna20240018

Impact of exosomal and cell-free circRNAs on cancer drug resistance

Heidi Schwarzenbach

Department of Gynecology, University Medical Center Hamburg-Eppendorf, 20246 Hamburg, Germany

E-mail: hschwarzenbach@me.com.

Abstract: Cancer is the most lethal disease in humans. Despite substantial advancements in cancer therapy during the last decades, the effectiveness of chemotherapeutic agents is limited since many patients develop drug resistance. Drug resistance leads to tumor recurrence and remains a major complication in cancer therapy. Modulated levels of circular RNAs (circRNAs) in various tumors are involved in drug resistance, tumor progression and recurrence. CircRNAs have been detected in different body fluids as well as in exosomes. They shuttle through the blood circulation as cell-free molecules or in exosomes, where they are transported to various cells to propagate malignancy. The current review describes the molecular factors that influence the response to targeted therapies, and summarizes the recent findings on the impact of extracellular circRNAs in drug resistance along with their targeted molecular pathways. Additionally, the potential clinical application of circRNAs as therapeutic agents as well as diagnostic and prognostic markers is also discussed.

Keywords: cancer; circRNAs; chemoresistance; plasma; serum; exosomes; therapy

1. Introduction

The main characteristic trait of cancer is the deregulation of the cell cycle leading to uncontrolled growth and proliferation of abnormal, malignant cells in an environment rich in activated stroma, growth and survival factors, DNA-damage-activating agents, and inflammatory cells [1]. Chronic oxygen deficiency and proliferative requirements of the established cluster of neoplastic cells cause angiogenesis. Angiogenesis comprises the development of new blood vessels derived from the existing vascular network, provides the tumor with oxygen, nutrients and growth factors, and permits tumor cells to spread to distant organs [2]. The dissemination of tumor cells is usually initiated by the epithelial–mesenchymal transition (EMT). In this process epithelial cells adopt mesenchymal features that exhibit enhanced migratory and invading capacity, and elevated resistance to apoptosis [3]. “The loss of epithelial markers, such as E-cadherin, claudins, and zonula occludens-1 is accompanied

with the enrichment of mesenchymal cell components, such as N-cadherin and vimentin, and triggers the disposal of epithelial cell polarity and the disturbance of cellular junctions, as well as the rearrangement of the cytoskeleton" [4]. This process allows the mesenchymal cells to infiltrate the surrounding microenvironment, in turn, to move through the blood and lymphatic circulation, and to invade to and metastasize in different organs of the body. As soon as the mesenchymal cells settle down at the distant sites, they adopt their epithelial features, again [5]. This multistep metastatic cascade remains the primary cause of death in patients who suffer from tumors and one of the leading causes of death, worldwide [6,7].

Due to an improved detection of locally confined tumors and adjuvant therapies that treat each step of the malignant disease, the 5-year survival of tumor patients could be extended in the last years. Regrettably, the extensive therapies are also associated with drug resistance resulting in increase in relapse rates. Hence, the emergence of chemoresistance is the main challenge for the clinician to ensure the effectiveness of anticancer therapies [8]. In the tumor immune microenvironment (TME), immune cells, including myeloid-derived suppressor cells, tumor-associated macrophages, tumor-associated neutrophils, and regulatory T cells, cytokines as well as cancer-associated fibroblasts, stellate cells and immunomodulators may cooperatively influence response to the treatment [9,10]. The complex molecular interaction of cancer cells with these TME cell populations may support cancer cell metabolism, repress drug delivery leading to enhanced immune suppression mechanisms and finally, to the development of resistance to chemo- and immunotherapy [9,11]. In addition, epigenetic changes including DNA methylation and histone modification also contribute to the development of drug resistance [12,13], including cis- and carboplatin resistance [14]. Therefore, new strategies and assays that target cancer-associated cell components and signalling pathways have to be designed to fight cancer cell survival.

Such therapies could be performed by circular RNAs (circRNAs) that participate in different stages of cancer, namely tumor initiation, progression, angiogenesis, EMT and metastasis. "CircRNAs are single-stranded non-coding RNAs (ncRNAs) and form a circular conformation via non-canonical splicing or back-splicing events" [15]. They are involved in different signaling pathways, regulating a variety of cellular events including cell division, apoptosis, cell mobility and metastasis [16]. They circulate as stable cell-free molecules or imbedded in exosomes through the bloodstream and lymphatic system [17]. Their shuttle in exosomes that are a part of TME and circulation as cell-free molecules allow them to propagate chemoresistance and metastasis. Besides, they may serve as biomarkers since their aberrant levels in blood correlate with the different tumor stages [7].

In this respect, the current review article deals with the regulatory network of extracellular circRNAs in cancer and their impact on cancer development and progression. Possible therapy strategies that apply circRNA inhibitors or mimics, or use circRNAs as biomarkers are also discussed.

2. Characteristics of circRNA

"About 80% of the genome is transcribed to ncRNAs. They comprise subgroups of miRNAs, circRNAs, lncRNAs (long non-coding RNAs), siRNA (small interfering RNAs) and piRNA (PIWI-interacting RNAs)" [18]. So far, over 100,000 circRNAs have been reported in human transcriptomes. They are characterized by a covalently closed loop structure without exposing 3′ and 5′ ends. "This stable ring structure precludes an early exonuclease-mediated degradation, resulting in half-life of over 48 hours which is much longer than that of linear RNAs with 10 hours" [19]. "CircRNAs are categorized in three subgroupes: exonic circRNAs (ecRNAs), exon-intron circRNAs (EIciRNAs) and circular intronic RNAs (ciRNAs)" [15]. They are usually expressed at low levels, but one gene can express multiple circRNAs, and have an impact on multiple signaling pathways and so, participate in different tumor stages. They circulate in different body fluids and can be transported by exosomes [20]. Their function comprises either the activation of gene transcription by binding to DNA polymerase II or conversely, the inhibition of mRNA translation. However, the majority of circRNAs serves as competing endogenous RNAs (ceRNAs), regulating the gene expression by sponging miRNAs [16,21] (Figure 1). In this respect, the first circRNA which was studied, was circ_RS-7 with more than 70 conserved miRNA binding sites [22]. MiRNAs can modulate post-transcriptionally the gene expression. In particular, they inhibit the translation through binding to the 3′untranslational region (UTR) of mRNA [23]. The ability of circRNAs to interact with miRNAs affects the binding of miRNAs to the 3′UTR of their mRNA target, leading to a translation of the mRNA performed by the ribosomes and not interfered by miRNAs. Thus, circRNAs may abrogate the oncogenic or tumor suppressive behavior of miRNAs [24]. A further particular function of circRNAs is that they can associate with circRNA binding proteins to regulate the translocation of certain proteins, implying the creation of an altered cellular protein expression profile [25].

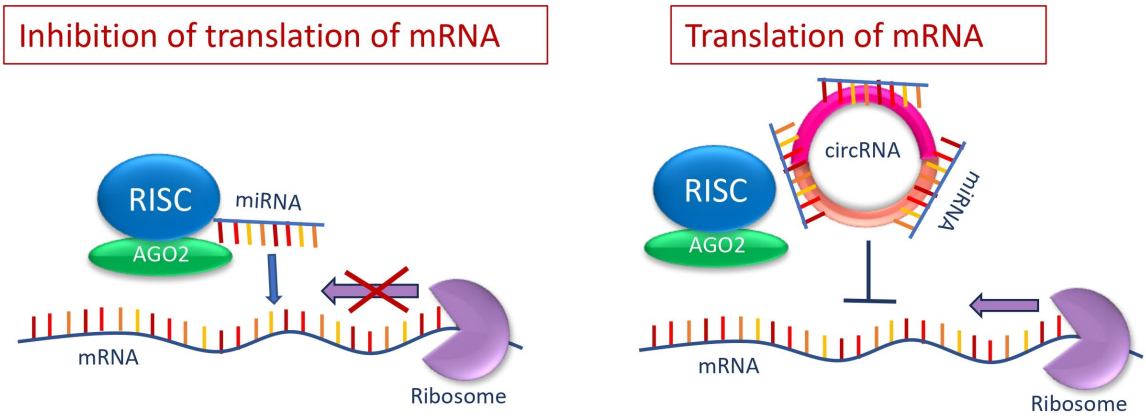

Figure 1. Mechanism of action of circRNAs and miRNAs on translation.

In the RNA-induced silencing complex (RISC), including argonaut protein AGO2, miRNA binds to the 3′end of their mRNA target, leading to the inhibition of translation by the ribosome. The binding of circRNA to the miRNAs abrogates this inhibition by miRNA.

3. Biogenesis of circRNAs

CircRNAs are generated during the RNA splicing process. Four classical regulatory models define the configuration of circRNAs [26]. 1) “In the lariat-driven circularization model, pre-mRNA is folded to bring nonadjacent exons in close proximity to each other. This initiates exon-skipping and back-splicing. The subsequent splicing which removes introns of the formed EIciRNA leads to ecRNA” [27]. 2) “In the intron-pairing-driven circularization model, base pairing of long flanking complementary introns containing Alu elements activates back-splicing. In this process, a downstream 5′ splice site is linked and ligated with an upstream 3′ splice site by a 3′-5′ phosphodiester bond at the junction site.” 3) In the RNA binding protein (RBP)-driven circularization model, RBPs are essential proteins in the formation of EciRNAs. As regulators of circRNA synthesis, more than a dozen RBPs have been identified. RBPs bind to flanking introns at both ends of an exon and get them together for back-splicing. 4) In the ciRNA biogenesis of intronic circRNAs, the lariat structure usually plays a key regulatory role. “Intron lariats are degraded by debranching enzymes, but a specific pre-mRNA structure consisting of 7 GU elements at the 5′-end and 11 C elements near the branch point at the 5′ end allows introns to escape debranching and to form a lariat structure to become a ciRNA” (Figure 2) [27].

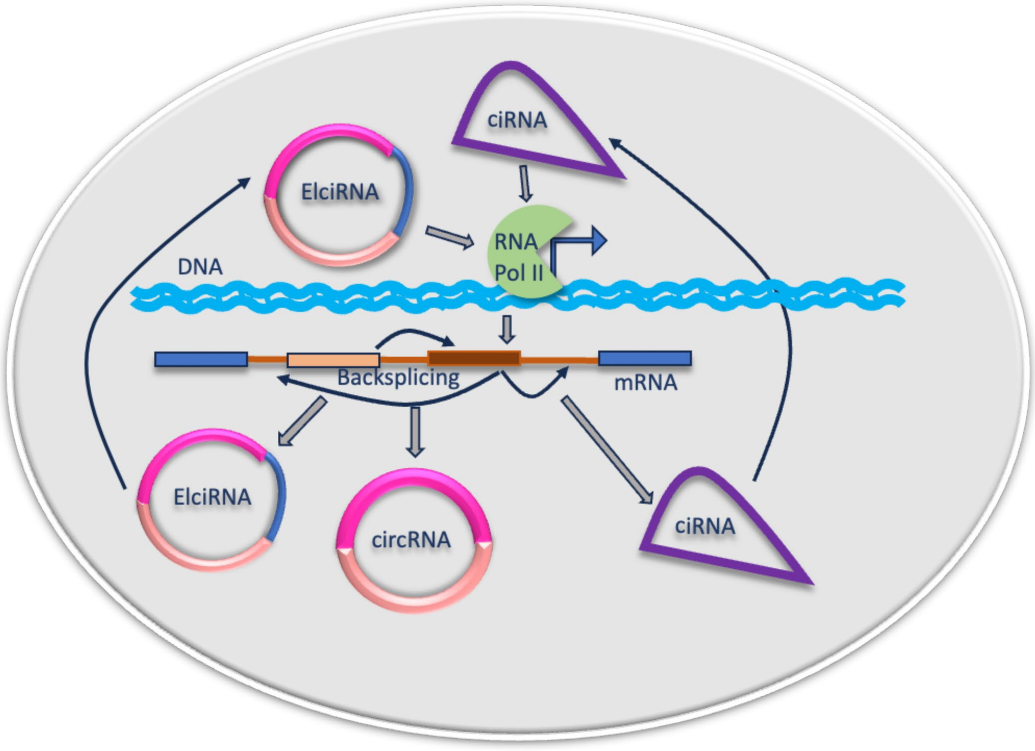

Figure 2. Biogenesis of cirRNAs.

Essential components of the biogenesis of circRNAs are depicted and described in more detail in the text. As shown, ElciRNA and ciRNA activate the transcription by RNA polymerase II (RNA Pol II).

4. Blood circulation and exosomes

In 1948, the presence of nucleic acids in blood was detected and described for the first time by Mendel and Métais [28]. "In 2013, Crowley *et al.* [29]. used the definition of liquid biopsy for the first time which was originally referred to plasma or serum, but has now been extended to include fluids, such as sputum, urine, saliva, breast milk, peritoneal fluid, bronchial lavage, cerebro-spinal fluid and seminal fluid".

Carcinogenesis is caused by deregulated apoptotic processes and alterations in proliferative behavior, triggering increased levels of circulating cell-free DNA and RNAs, including circRNAs in the adjacent body fluids of cancer patients. The physiological events that lead to this release into the human blood encompass processes, such as cell apoptosis and necrosis along with active cell secretion [30,31]. "Different sources, including the primary tumor, circulating tumor cells (CTCs), micrometastatic deposits and normal cell types, such as hematopoietic and stromal cells contribute to this release" [32]. Thus, both tumor cell- and normal cell-associated circRNAs circulate in the blood of cancer patients. Apart from these cell-free components, exosomes also circulate in the bloodstream [15,20].

In addition, high levels of exosomes have been detected in the blood circulation [33]. Exosomes are extracellular vesicles which transport informative molecules including proteins, RNAs, DNA and lipids from cell to cell via varying distances. In this respect, exosome-mediated intercellular communication has been reported to be a mechanism of drug resistance in cancer. This exosome shuttle results in the biological modification of the recipient cell which takes up the exosomes [34]. In particular, the uptake of exosomes containing oncogenic material derived from cancer cells in the recipient healthy cells may influence the biological character of these cells and convert them into malignant cells [34]. This transfer process is especially important for the propagation of genetic information that leads to tumor progression. Likewise, exosomes are ideal carrier molecules for the treatment of tumors to bring anti-tumor compounds to the cancer. This cell-to-cell communication facilitated by exosomes can be applied in the therapy of drug resistance. Since exosomes carry on their surface cell-specific markers and immune-regulatory receptors, the uptake of the exosomes into the recipient cells is facilitated. [35,36].

To date, the importance of exosomes as intercellular communicators has been described for various tumors in numerous studies [34]. They are involved in different processes, such as drug resistance, immune evasion, EMT, angiogenesis and metastasis [36]. For example, exosomes containing functional proteins and ncRNAs are secreted from tumor and stromal cells into the tumor microenvironment (TME). They remodel TME and mediate drug resistance by supporting drug efflux and metabolism, as well by inducing pro-survival signaling pathways and stem-like properties [37]. Cancer stem cells secrete exosomes to modulate immune checkpoint molecules to evade immune surveillance [38]. Immune cell-derived exosomes are ideal components for an immunotherapy. Due to their biocompatibility, they display less toxicity and reduced immunogenicity [39,40]. Furthermore, hypoxia is a critical feature of the TME and induces metabolic reprogramming of tumor cells which stimulate the secretion of hypoxic exosomes. The release of these vesicles into the TME

supports immune evasion and cancer progression by recruiting protumor and inhibiting antitumor immune cells [41]. In ovarian cancer, exosomes promote peritoneal metastasis by inducing EMT in peritoneal mesothelial cells, modifying the extracellular matrix and activating angiogenesis which permits the dissemination of cancer cells across the peritoneal cavity [42]. Interestingly, experimental studies demonstrate the association of EMT with the secretion and sorting pathway of exosomes in esophageal cancer cells. The regulatory effect of EMT on exosomes in the quantity and contents seems to be exerted by miRNAs that modify intracellular transcription levels and are involved in the specific sorting mechanism of exosomes [43].

To sum up, these few studies inherently reveal the involvement of exosomes in the propagation of oncogenic signals to stimulate tumor progression and metastasis.

Finally, the biogenesis of exosomes has been described in numerous articles. The begin is initiated by the endocytosis of microvesicles by cells and leads to fusion of these vesicles to early endosomes which develop into late endosomes or lysosomes. Late endosomes mature into MVBs (multivesicular bodies) containing small intra-vesicular vesicles (IVLs) through membrane in-folding processes. The association of MVBs with the cell membrane leads to the release of IVLs into the extracellular area, now called exosomes [44].

5. Drugs in therapies

After initially positive treatment outcomes, the effectiveness of the applied drugs weakens and is therefore not permanent. Through genetic alterations, such as mutations or deletions, and selection, tumor cells develop new genetic variants that counteract the therapeutic effect of the drugs, leading to the development of chemoresistance. The underlying mechanisms are complex. Chemoresistance covers a variety of transporters that participate in the active transport of antitumor agents out of the cells [45,46]. Deregulated levels of intracellular glutathione and metallothioneine may bind and sequester platinum components [47]. In addition, altered DNA repair pathways and reduced expression of pro-apoptotic proteins, altered expression levels, localization, or activity may severely reduce the cellular drug accumulation [8]. Besides, the modulations are associated with epigenetic changes of DNA methylation and histone modifications [48].

A variety of anticancer drugs and combinations of them are used in cancer therapy (Table 1). For example, cisplatin is used for different tumor types. It covalently binds to purine bases and introduces monoadducts or inter- and intra-strand crosslinks leading to disruption of the replication machinery, G2/M cell arrest and cell death by apoptosis or necrosis. Moreover, it may induce oxidative stress by enhancing mitochondrial reactive oxygen species and reducing intracellular antioxidants. However, it has severe side effects for the patients, including nephrotoxicity and acute kidney injury [49].

Paclitaxel and docetaxel belong to the group of taxanes. Cancer types, such as bronchial, breast, ovarian and prostate carcinoma are treated with paclitaxel in combination with other cytostatics, such as cisplatin. Following binding to β-tubulin, it inhibits and thus, blocks mitotic cell division in the G2 and M phases [50].

Table 1. Drugs and their main features.

Drugs	Function	Effect	Ref.
Cisplatin	Binding to purines	DNA damage	[49]
Taxanes	Inhibition of breakdown of spindle fibers	Inhibition of mitosis	[50]
Doxorubicin	DNA intercalator inhibitions of topomerase II	Inhibition of DNA/RNA synthesis	[51]
5-fluorouracil	inhibition of thymidylate synthase	Inhibition of DNA synthesis	[52]
Oxaliplatin metabolites	DNA crosslinks	Inhibition of DNA synthesis	[52]
IgG antibody anti-PD	check point inhibitor	Immune response	[53]
Abiraterone	inhibitor of CYP17A1	Inhibition of testosterone/estrogen production	[54]
Enzalutamide	Inhibition of the binding of receptor.	Inhibition of DNA replication	[54]
Gemcitabine	Pyrimidine analogues	Inhibition of DNA replication	[55]
Temozolomide	Alkylating agent	Inhibition of DNA replication	[56]
Bortezomib	Proteasome inhibitor	Inhibition of proteolysis	[57]
Gefitinib, imatinib, lapatinib	Tyrosine kinase inhibitors	Inhibition of signaling pathways	[58]
Sorafenib, vemurafenib	Protein kinase inhibitors	Inhibition of signaling pathways	[58]
Vemurafenib	BRAF inhibitor	Inhibition of Ras/Raf/MAPK signaling pathway	[58]

Doxorubicin belongs to the anthracycline group and is used to treat various malignant tumors. It blocks DNA and RNA synthesis in the S phase of the cell cycle. Its action includes two main mechanisms. It intercalates the DNA, inserting itself between two neighboring nucleotides and thereby blocking transcription. In addition, it inhibits topoisomerase II that is responsible for the separation of intertwined DNA daughter strands after DNA replication and before mitosis. Likewise, actinomycin D is also an intercalating agents and acts in a similar manner to doxorubicin [51].

FOLFOX is a chemotherapy regimen and used to treat colorectal cancer (CRC). It consists of a combination of folinic acid (FOL), 5-fluorouracil (5-FU) and oxaliplatin (OX). 5-FU inhibits thymidylate synthase, a key enzyme in pyrimidine biosynthesis. FOL is applied to increase the cytotoxic activity of 5-FU. It potentiates the inhibition of thymidylate synthase by increasing intracellular folate concentration. Oxaliplatin, the third drug in this combination, belongs to the class of platinum derivatives. It prevents or delays the development of platinum resistance in tumor cells. In addition, oxaliplatin metabolites react with the DNA and form cross-links between the DNA strands [52].

Anti-PD1 is a check point inhibitor and belongs to a class of IgG antibodies that target the transmembrane protein programmed cell death protein 1 (PD1). Activation of this receptor on cytotoxic T cells causes an increased immune response to tumor tissue [53].

Abiraterone belongs to the steroid group and is used in hormone therapy. It is a selective inhibitor of the enzyme CYP17A1 which normally catalyzes both testosterone and estrogen production. If this synthesis is blocked, the testosterone concentration drops which is important in the treatment of prostate cancer [54].

Enzalutamide belongs to the antiandrogen class. It is used to treat advanced prostate cancers. Competitive inhibition of the binding of androgens to the androgen receptor by

enzalutamide prevents the translocation of the activated receptor into the cell nucleus and the inhibition of binding of the receptor to DNA, resulting in the prevention of DNA replication [54].

Gemcitabine belongs to the group of pyrimidine analogues and is used to treat diverse tumors. It is first phosphorylated in the body and converted into its biologically active form of gemcitabine triphosphate. In this form it can be incorporated in the DNA strand during the DNA replication [55].

Temozolomide is used for the simultaneous, adjuvant and palliative therapy of glioblastomas and forms of astrocytoma in combination with radiation therapy. It is an alkylating agent. The triazene derivative is converted into its active form of mono-methyl-triazenyl-imidazole carboxamide (MTIC) in the body. MTIC predominantly alkylates at the O-6 position of guanine with additional alkylation at the N-7 position. These modifications of DNA lead to inhibition of the DNA synthesis [56].

Bortezomib is used to treat multiple myeloma. It is a proteasome inhibitor and thus, inhibits the proteolysis [57].

Gefitinib, imatinib and lapatinib belong to the group of tyrosine kinase inhibitors (TKI), while sorafenib and vemurafenib belong to the group of protein kinase inhibitors that target different receptor kinases. These drug with the suffix “nib” are small molecules that pass through the cell membrane and bind to kinases inside the cell, blocking different signaling pathways [58].

Gefitinib is largely used to treat bronchial carcinomas. It selectively inhibits the epidermal growth factor receptor (EGFR) with its activating mutated tyrosine kinase, thereby suppressing tumor cell growth.

Imatinib is applied to treat chronic myeloid leukemia (CML) and gastrointestinal stromal tumors (GIST). CML is triggered by reciprocal translocation between chromosome 9 and chromosome 22 at defined break points resulting in formation and constant activity of the so-called Philadelphia chromosome. Its translation into a BCR-ABL fusion protein leads to proliferation and reduced apoptosis of the leukemia cells. If the BCR-ABL gene harbors point mutations, patients may develop imatinib resistance within the first three years.

Lapatinib is used to treat breast tumors that express human epithelial receptor 2 (HER2) and EGFR on their cell surface. It is largely used as a second-line therapy in combination with capecitabine or trastuzumab for advanced or metastatic breast cancer that overexpresses theses receptors that harbor strongly proliferative activity.

Sorafenib is a multitargeted small tyrosine kinase inhibitor (TKI) molecule affecting the intracellular component of the transmembrane vascular epithelial growth factor receptor (VEGFR) 1, 2 and 3, Raf kinase, platelet-derived growth factor receptor (PDGFR), Fms-like tyrosine kinase-3 (Flt-3), c-Kit and p38. It is used, among others, to treat advanced kidney cancer and hepatocellular carcinoma (HCC). The inhibition of the RAF kinase by sorafenib leads to the interruption of different signaling pathways that stimulate tumor progression.

Vemurafenib is primarily used to treat metastatic melanoma, and inhibits serine–threonine and tyrosine protein kinases. It is a selective inhibitor of BRAF that participates in

the Ras/Raf/MAPK signaling pathway. BRAF mutations are found in approximatively half of all melanomas. Vemurafenib specifically targets the V600 mutation of BRAF.

6. Major signaling pathways involved in drug resistance and regulated by circRNAs

To date, numerous circRNAs regulate cellular functions and control the development of cancer via their participation in different signaling pathways. The interaction between circRNAs and the pathways mainly occurs by the ceRNA mechanism which comprises the activation or repression of the downstream components of the following pathways by sponging miRNAs [59–61].

6.1. PI3K/Akt/mTOR signaling

"In the phosphoinositide 3 kinase (PI3K)/Akt/mammalian (or mechanistic) mammalian target of rapamycin (mTOR) cascade, PI3K phosphorylates phosphatidylinositol 4,5 bisphosphate (PIP_2) to phosphatidylinositol 3,4,4-triphosphate (PIP_3) which in turn leads to the phosphorylation of the serine/threonine kinase Akt" [62]. This results in diverse downstream effects, including activation of cAMP response element-binding protein (CREB), inhibition of p27 and activation of mTOR. The pathway is inhibited by PTEN (phosphatase and tensin homologue) [63]. Aberrant activation of the pathway leads to decreased apoptosis along with increased cell proliferation. Many factors, among others EGF, insulin-like growth factor-1 (IGF-1) and insulin, reinforce the signal of the PI3K/AKT/mTOR pathway [64].

In addition, circRNAs have an important impact on this pathway to mediate drug resistance by [59]. For example, Wang *et al.* [65] showed that circ_UBAP2 was a ceRNA for miR-300 to upregulate the expression of anti-silencing function 1B histone chaperone (ASF1B). In turn, ASF1B activated the PI3K/AKT/mTOR signaling pathway to facilitate the cisplatin resistance of triple-negative breast cancer (TNBC) cells. Li *et al.* [66] also investigated TNBC cells which do not express estrogen and progesterone receptors as well as HER2 and are, therefore, particularly aggressive tumor cells. This laboratory showed that circ_0000199 targeted and negatively regulated miR-613 and miR-206, leading to depression and activation of the PI3K/Akt/mTOR signaling pathway, and enhancing TNBC chemoresistance.

6.2. Wnt signaling

"The Wnt signaling pathway is branched into two routes: the β-catenin dependent (canonical) and the β-catenin independent (non-canonical) pathways" [67]. Binding of Wnt proteins to Frizzled receptors and low-density lipoprotein receptor-related protein families on the cell surface transmits a signal to β-catenin via several cytoplasmic components. In turn, β-catenin forms a complex with the transcription factor TCF in the nucleus, stimulating the transcription of Wnt target genes [68]. In cancer, the deregulation of the signaling pathway leads to a reinforced cell proliferation, differentiation and migration. "There are multiple

aberrations in this pathway, including mutations in β-catenin or other key components of the cascade, as well as hypermethylation and silencing of gatekeeper antagonists [69], such as the secreted frizzled-related protein (SFRP) and dickkopf (DKK), or overexpression of Wnt ligands or receptors" [70].

Besides, circRNAs also influence the Wnt signaling pathway. For example, Li *et al.* [71] reported that circ_TTLL13 activated the Wnt/β-catenin signaling pathway by regulating the oxidized LDL receptor 1 (OLR1) to promote temozolomide resistance of glioma cells. As shown in the study by Zhou *et al.* [72], circ_0055412 was upregulated in glioma cells. Circ_0055412 supported cisplatin resistance of glioma cells via stabilizing gelsolin like (CAPG) mRNA, modulating the Wnt/β-catenin signaling pathway. In this context, circ_0055412 served as a sponge for miR-330 and activated nuclear factor of activated T cells 3 (NFATC3) expression to stimulate the transcription of catenin beta 1. Furthermore, in osteosarcoma, cells, Gong *et al.* [73] found that circ_UBAP2 activated the cisplatin resistance by the Wnt/β-catenin signaling pathway. Here, miR-506-3p was sponged by circ_UBAP2 which led to the increasing expression of semaphorins 6D (SEMA6D). Thus, the active role of circ_UBAP2 promoted progression of cisplatin in osteosarcoma.

6.3. JAK/STAT signaling

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) starts with the binding of cytokines, such as interleukins and growth factors, namely PDGF, transforming growth factor β (TGF-β) and fibroblast growth factor (FGF), to their corresponding receptors resulting in receptor dimerization and recruitment of JAKs. In turn, activated JAKs stimulate tyrosine phosphorylation of the receptors and formation of binding sites for STATs. Phosphorylated STATs detach from the receptor to create homodimers or heterodimers which enter the nucleus to bind to DNA and regulate transcription. The JAK/STAT signaling pathway may be negatively regulated by the protein inhibitor of activated STAT (PIAS), the suppressor of cytokine signaling CIS (cytokine-inducible SH2 protein)/SOCS (suppressors of cytokine signaling), and the protein tyrosine phosphatase (PTP). This rapid membrane-to-nucleus signaling affects different facets of the immune system [74].

CircRNAs may also play a role in the JAK/STAT signaling pathway, and it is assumed that they support drug resistance by this pathway [75].

6.4. Notch signaling

The Notch pathway starts with two cleavages of the Notch intracellular domain (NICD) which is discharged into the cytoplasm. Following entering the nucleus, NICD binds to the ubiquitous transcription factor CSL, and switches a large co-repressor complex into a transcription activating complex. "The complex stimulates the transcription of Notch target genes, such as p21, cyclin D1 and 3, c-myc and members of the NF-κB family". Deregulation of the Notch pathway in cancer leads to increased cell proliferation, and reduced differentiation and apoptosis. Among others, it is triggered by a receptor-ligand binding between two adjacent cells, effecting a conformational change of the Notch receptor [76].

Regarding the role of circRNAs in the Notch signaling pathway, the study by Yao *et al.* [77] indicated the participation of circ_FAT1 in this signaling pathway to promote oxaliplatin resistance in breast cancer. In oxaliplatin-resistant cells, circ_FAT1 targeted miR-525-5p to enhance spindle and kinetochore-associated complex subunit 1 (SKA1). In addition, this laboratory also found that circFAT1 could confer oxaliplatin resistance in breast cancer by regulating miR-525-5p/SKA1 via the Wnt pathway. Thus, both signaling pathways were regulated by circ_FAT1 in a similar manner.

6.5. NF-κB signaling

Initiation of the canonical pathway by Toll-like microbial pattern recognition receptors (TLRs) and proinflammatory cytokines, such as tumor necrosis factor α (TNFα) and interleukin 1 (IL-1), leads to activation of the transcription factor RelA that regulates the expression of proinflammatory and cell survival genes. The alternative NF-κB pathway is activated by the membrane proteins lymphotoxin beta (LTβ) and CD40L as well as the cytokine B cell activating factor (BAFF), and the receptor activator of NF-κB ligand RANKL, and results in stimulation of RelB/p52 complexes. Activation of the alternative pathway regulates genes involved in lymph-organogenesis and B-cell activation. The canonical and alternative pathways require different IκB kinase (IKK) subunits. IKKβ regulates activation of the canonical pathway, whereas IKKα stimulates the alternative pathway [78].

The involvement of circ_ZFR in the NF-κB signaling pathway was demonstrated by Zhou *et al.* [10] carrying out *in vivo* tumor xenograft experiments. In this study, circ_ZFR increased cisplatin resistance in hepatocellular carcinoma (HCC). Exosomes derived from cancer-associated fibroblasts delivered circ_ZFR to HCC cells, inhibited the STAT3/NF-κB pathway, and promoted HCC chemoresistance.

To date, the above studies have shown that circRNAs serve as sponge for miRNAs. They mainly exert their influence on the different signaling pathways through their binding to miRNAs, to prevent the inhibitory effect of miRNAs on their targets within the signaling pathways. Thus, the mode of action mediated by miRNAs is abrogated by circRNAs, suggesting that signaling pathways may undisturbedly proceed – provided there are no impact through other factors.

Conclusively, the involvement of circRNAs in the signaling pathways may provide new strategies for the prevention and treatment of chemoresistance.

7. Extracellular circRNAs in drug resistance

In order to characterize and determine the aberrant expression levels of circRNAs in cancer patients, RNA microarrays or sequencing followed by real-time quantitative reverse transcription PCR (RT-PCR) are commonly applied [79,80]. Current investigations have been shown that circRNAs mainly inhibit miRNAs and so, abrogate the inhibitory effect on translation by miRNAs (Figure 1). Upregulated, cell-free and exosomal circRNAs which circulate in blood of patients with different tumor types have critical functions in

tumorigenesis and are important key molecules in the regulation of cellular behavior. Especially, they are involved in the clinical resistance to different drugs [15].

They participate in and modulate different signaling pathways (Table 2). For example, exosomal circ_PIP5K1A derived from serum increased progression of non-small-cell lung carcinoma (NSCLC) and promoted resistance to cisplatin by regulating the miR-101/ABCC1 axis. In NSCLC tissues and serum samples, circ_PIP5K1A and the ATP binding cassette ABCC1 were overexpressed whereas miR-101 was downregulated. In this context, circ_PIP5K1A stimulated ABCC1 expression by sponging miR-101 [81]. Likewise, high levels of exosomal circ_0076305 increased the expression of ABCC1, also leading to cisplatin resistance in NSCLC. In this case, miR-186 was targeted by circ_0076305 [82]. In addition, the levels of circ_PVT1 which were upregulated in osteosarcoma (OS) tissues and serum correlated with the expression of ATP binding cassette ABCB1, and the resistance to doxorubicin and cisplatin of OS cells [83]. These ABC transporters which are membrane-bound proteins transport cisplatin, doxorubicin and other drugs out of the cell, to impede these drugs to covalently bind with purine bases and to intercalate DNA. Thus, their mode of action prevents DNA damage and the toxicity that is exerted by the drugs on the cells and contributes to the drug resistance of tumor cells [84].

In colorectal cancer (CRC), circ_0006174 regulated chemoresistance of doxorubicin via exosomes. High levels of circ_0006174 were detected in exosomes derived from doxorubicin-resistant CRC cells, and could in turn increase doxorubicin resistance via the exosomal intercellular transfer. The effect of exosomal circ_0006174 on doxorubicin resistance was achieved by targeting miR-1205 which resulted in upregulating cyclin D2 (CCND2) [85]. Cyclins are G1/S cell cycle checkpoint proteins and play an essential role in defining cell cycle exit and progression. In response to mitogenic stimulation, CCND2 is expressed through the PI3K-Akt pathway that stimulates the synthesis and promotes the stability of cyclin D [86].

In gastric cancer (GC), circ_0091741 which was transferred by cell-derived exosomes induced autophagy and resistance to oxaliplatin which forms DNA crosslinks in GC cells. Circ_0091741 hindered the binding of miR-330-3p to tripartite motif containing 14 (TRIM14) and consequently, increased the expression of TRIM14. Thereupon, TRIM14 activated the Wnt/β-catenin signaling pathway, leading to increased autophagy and oxaliplatin resistance of GC cells [87]. Furthermore, TRIM14 was also a target of miR-198 in glioma. Significantly upregulated circ_0005198 in serum, as well as in tissue supported resistance to the alkylating agent temozolomide, increased the cell proliferation and inhibited the apoptosis of temozolomide-resistant glioma cells. This was attained by that miR-198 was sponged by circ_0005198, leading to the stimulation of TRIM14 [88].

Circ_ZFR which was highly expressed in hepatocellular cancer (HCC)-associated fibroblasts (CAFs) and exosomes released from the CAFs, could regulate cisplatin resistance of the HCC cells. CAFs-derived exosomes delivered circ_ZFR to HCC cells, inhibited the STAT3/NF-κB pathway, and promoted HCC development and chemoresistance [10].

Increased levels of circ_BACH1 expression were observed in paclitaxel-treated breast cancer-derived exosomes and tissue. The transfer of these exosomes promoted cell viability,

stemness, migration and angiogenesis through upregulated circ-BACH1. In this context, circ_BACH1 targeted miR-217 to upregulate GTPase-activating SH3 domain-binding protein 2 (G3BP2), resulting in resistance to paclitaxel, which inhibits breakdown of spindle fibers [89].

High levels of circ_0010467 were detected in serum exosomes as well as in cells and tissue of cisplatin-resistant osteosarcoma patients, and positively associated with advanced tumor stage and poor prognosis of these patients. Circ_0010467 supported the platinum resistance by activating tumor cell stemness, and acted as a miR-637 sponge to inhibit the repressive impact of miR-637 on leukemia inhibitory factor (LIF). In turn, LIF activated the STAT3 signaling pathway. Conversely, the RNA binding protein AUF1 could promote the biogenesis of circ_0010467 in osteosarcoma [90].

In cisplatin-resistant esophageal cancer tissues and cells, the levels of circ_0000337 and JAK2 were increased, whereas those of miR-377 were decreased. Cisplatin-resistant esophageal cancer cells secreted circ_0000337-containing exosomes which promoted cisplatin resistance, cell growth and metastasis of cisplatin-sensitive esophageal cancer cells. Mechanical analyses revealed that circ_0000337 acted as a sponge of miR-377 to regulate JAK2 expression. Thereupon, the JAK2 cell signal promoted growth and metastasis of esophageal cancer [91].

Circ_NPM1 was abundantly expressed in serum samples from acute myeloid leukemia (AML) patients, whereas miR-345 was downregulated in the serum. The inhibition of miR-345 by circ_NPM1 resulted in the activation of frizzled-5 (FZD5). Conversely, FZD5 overexpression could block the function of miR-345 restoration. This miR-345-5p/FZD5 axis mediated by circ-NPM1 reinforced doxorubicin chemoresistance of AML cells [92].

To sum up, these examples show that exosomes can transfer circRNAs from cell to cell to propagate drug resistance, converting sensitive into resistant cells. Thus, this spreading of chemoresistance by circRNA-containing exosomes may be a key target for overcoming drug resistance in cancer. In addition, cell-free circRNAs that circulate in blood may also contribute to this process.

Table 2. Upregulated plasma, serum and exosomal circRNAs in drug resistance of different cancer types.

CircRNAs	Target	Cancer	Source	Drug	Ref.
circ_VMP1	miR-524/METTL3 /SOX2	NSCLC	serum	cisplatin	[93]
circ_0008928	miR-488/HK2	NSCLC	S-exo	cisplatin	[94]
circ_PIP5K1A	miR-101/ABCC1	NSCLC	S-exo	cisplatin	[81]
circ_0076305	miR-186/ABCC1	NSCLC	C-exo	cisplatin	[82]
circ_0046264	-	NSCLC	serum	cisplatin	[95]
circ_0005962	-	NSCLC	serum	paclitaxel	[96]
circ_USP7	miR-934/SHP2	NSCLC	P-exo	anti-PD1	[97]
circ_102481	miR-30a/ROR1	NSCLC	S-exo	EGFR-TKI	[98]
circ_0008057	miR-370/PLk1	NSCLC	serum	gefitinib	[99]
circ_SH3PXD2A	miR-375/YAP1	SCLC	S-exo	cisplatin	[100]
circ_0041150	-	SCLC	serum	actinomycin D	[101]
circ_0030591, 0040348	-	LUAD	plasma	gefitinib	[102]

Table 2. *Cont.*

CircRNAs	Target	Cancer	Source	Drug	Ref.
circ_DNER	miR-139/ITGB8	LUAD	P-exo	paclitaxel	[103]
circ_ZNF451	FXR1-ELF4-IRF4	LUAD	S-exo	anti-PD1	[104]
circ_0000338	-	CRC	C-exo	FOLFOX	[105]
circ_0004085	GRP78, ATF6p50	CRC	plasma	oxaliplatin /5-FU	[106]
circ_ATG4B	-	CRC	C-exo	oxaliplatin	[107]
circ_0005963	miR-122/PKM2	CRC	C-exo	oxaliplatin	[108]
circ_0006174	miR-1205/CCND2	CRC	C-exo	doxorubicin	[85]
circ_0063526	miR-449a/SHMT2	gastric	S-exo	cisplatin	[109]
circ_PVT1	miR-30a/YAP1	gastric	S-exo	cisplatin	[110]
circ_LDLRAD3	miR-588/SOX5	gastric	C-exo	cisplatin	[111]
circ_50547	miR-217/HNF1B	gastric	S-exo	oxaliplatin	[112]
circ_0091741	miR-330/TRIM14	gastric	C-exo	oxaliplatin	[87]
circ_0032821	miR-5157SOX9	gastric	C-exo	oxaliplatin	[113]
circ_WDR62	miR-370/MGMT	glioma	C-exo	temozolomide	[114]
circ_0043949	miR-876	glioma	C_exo	temozolomide	[115]
circ_HIPK3	miR-421/ZIC5	glioma	C-exo	temozolomide	[116]
circ_0042003	-	glioma	C-exo	temozolomide	[117]
circ_0005198	miR-198/TRIM14	glioma	serum	temozolomide	[88]
circ_DLGAP4	miR-143/HK2	NB	C-exo	doxorubicin	[118]
circ_ZFR	STAT3/NF-κB	HCC	C-exo	cisplatin	[10]
circ_UHRF1	miR-449c/TIM-3	HCC	P-exo	anti-PD1	[119]
circ_0000615	-	HCC	serum	sorafenib	[120]
circ_0001275	-	prostate	plasma	enzalutamide	[121]
circ-SFMBT2	miR-136-5p/TRIB1	prostate	S-exo	docetaxel	[122]
circ_CEP112/FAM13A /BRWD1/VPS13C /MACROD2	-	mCRPC	P-exo	abiraterone	[123]
circ_ZNF91	miR-23b	PC	C-exo	gemcitabine	[124]
circ_103801	-		OSC-exo	cisplatin	[125]
circ_PVT1	ABCB1	OS	serum	doxorubicin, cisplatin	[83]
circ_BACH1	miR-217/G3BP2	breast	C-exo	paclitaxel	[89]
circ_MMP11	miR-153/anillin	breast	C-exo	lapatinib	[126]
circ_0010467	miR-637/LIF/STAT3	ovarian	S-exo	cisplatin	[90]
circ_0000337	miR-377/JAK2	esophageal	C-exo	cisplatin	[91]
circ_0074269	miR-485/TUFT1	cervical	C-exo	cisplatin	[127]
circ_NRIP1	miR-515-/IL-25	NPS	serum	cisplatin	[128]
circ_LTBP2	miR-338	iCCA	S-exo	gemcitabine	[129]
circ_0001005	-	melanoma	C-exo	vemurafenib	[130]
circ_NPM1	miR-345/FZD5	AML	serum	doxorubicin	[92]
circ_MYC	-	MM	S-exo	bortezomib	[131]
circ_0009910	miR-34a	CML	serum	imatinib	[132]
circ_0058493	miR-548b	CML	C-exo	imatinib	[80]

ABCC1/ABCB1, ATP binding cassette subfamily C/B member 1; AML, acute myeloid leukemia; CCND2, cyclin D2; C-exo, cell-derived exosomes; CML, chronic myeloid leukemia; CRC, colorectal cancer; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; FOLFOX, folinic acid, fluorouracil,

oxaliplatin; FU, fluorouracil; FZD5, frizzled receptor 5; G3BP2, GTPase-activating protein-binding protein 2; HCC, hepatocellular cancer; HK2, hexo kinase 2; HNF1B; hepatocyte nuclear factor 1 homeobox B; iCCA, intrahepatic cholangiocarcinoma; IL-25, interleukin-25; LIF, leukemia inhibitory factor; LUAD, lung adenocarcinoma, mCRPC, metastatic castration-resistant prostate cancer; METTL3, N6-adenosine-methyltransferase complex catalytic subunit; MM, multiple myeloma; NB, neuroblastoms; NPS, nasopharyngeal carcinoma; NSCLC, non-small cell lung cancer; OS, osteosarcoma; PC, pancreatic cancer; PD1, programmed death 1; P-exo, plasma exosomes; PLk1, polo-like-kinase 1; PKM2, pyruvatkinase M2; ROR1, receptor tyrosine kinase-like orphan receptor 1; S-exo, serum exosomes; SCLC, small cell lung cancer; SHP2, Src homology region 2 (SH2)-containing protein tyrosine phosphatase 2; SOX, SRY-box transcription factor; TRIB1, tribbles homolog 1; TRIM14, tripartite motif containing 14; Tuftelin 1, TUFT1.

8. Clinical significance and therapeutic strategies

Due to their high stability and long half-life which is based on their ring structure, and their abundance in body fluids, circRNAs have great potential for serving as non-invasive biomarkers. Their differentially expressed levels in the blood circulation may correlate with therapy course and clinical parameters of the cancer patients. Thus, their aberrant cancer-associated expression makes circulating circRNAs to ideal diagnostic and prognostic biomarkers to be measured in the blood circulation of cancer patients [133]. Moreover, circRNAs are abundantly packaged in exosomes which communicate with various cells and propagate circRNAs from cell to cell, leading to drug resistance and tumor progression. An important strategy of the development of novel therapeutic approaches for cancer is the targeting of exosome-containing circRNAs [15,17].

As detailed reviewed by He *et al.* [134], assays have been established to target oncogenic circRNAs for therapeutic purposes. These technologies comprise small interfering RNA (siRNA), short hairpin RNAs (shRNAs), antisense oligonucleotides and CRISPR/cas13a. Concerning this matter, siRNAs at size of 21-23 nucleotides bind to circRNAs by complementary pairing and integrate them into the RISC to be cleaved. ShRNAs consisting of a loop and base-paired stems are processed into siRNA. Antisense oligonucleotides are also able to bind to circRNAs through complementary pairing. Because of their longer length, they can efficiently block protein interaction sites on circRNAs. The CRISPR/cas13a system applies small guide RNAs to direct the Cas9 nuclease to bind to and cleave DNA. During circRNA biogenesis, CRISPR/Cas9 can degrade circRNAs and so, disrupt the pairing of introns flanking the circularized exons.

Delivery systems to target circRNAs apply adenoviral and lentiviral vectors as well as nanoparticles. Nanoparticles that range from 10 to 1000 nm at size are generated of organic materials, e.g., phospholipid and polymers or inorganic materials, e.g., gold and metal oxides. Lipid nanoparticles (LNPs) are the most frequently used nanoparticle delivery systems. They can encapsulate siRNAs and bind to specific cells by targeting endogenous or exogenous ligands. Endocytosed LNPs release the siRNAs into the cytosol to so, reach their targets. Since nanoparticles cannot enter the nucleus, this transfer is restricted to target circRNAs in the cytoplasm [134].

Exosomes also serve as delivery systems and have a high biocompatibility, low immunogenicity and high chemical stability [135]. Alike nanoparticle delivery systems, exosomes can defend their RNA content from degradation and activate cellular uptake. To date, a variety of exosome-delivered vaccines have been introduced into clinical trials, e.g., dendritic cell-derived exosomes (NCT01159288) and himeric exosomal tumor vaccines for recurrent or metastatic bladder cancer (NCT05559177) [136–138].

Considering the potential value of circRNAs as diagnostic and prognostic biomarkers and as therapeutic agents, several clinical trials that deal with oncogenic circRNAs have been introduced (https://www.chictr.org.cn/ and https://clinicaltrials.gov/).

9. Limitations of circRNAs in drug resistance

The main drawback of chemotherapy is that it may lead to the gradual transformation of chemo-sensitive cells to -resistant cells. Drug resistance is a complex process which includes altered drug targets, and is regulated by different mechanisms, such as drug efflux, inhibition of cell apoptosis and DNA repair, as well as autophagy [8,48,139]. Beside numerous factors that also contribute to drug resistance [8], deregulated circRNAs participate in this process, to stimulate different cancer-associated signaling pathways that cross-talk among one another.

Limitations for a treatment of drug resistance referring to circRNAs is that not only one circRNA may be differentially expressed in drug resistance, but several circRNAs may be involved in this process [140]. This makes it especially difficult to determine which circRNA is propriate for a treatment of drug resistance. Since circRNAs are able to interfere different molecular processes, it is also challenging to determine the extent of their impact on the different cellular processes along with their exerted negative side effects. Notably, circRNAs have versatile functions. They may act as miRNA sponges and ceRNAs [24]. They harbor several miRNA binding sites that may target and inhibit several miRNAs. In addition, several circRNAs can target one miRNA. One circRNA is able to inhibit both oncogenic miRNAs, and tumor suppressive miRNAs as well. This complicated network of ncRNAs may influence different signaling pathways that cross-talk with each other and lead to a wide variety of cellular changes [16]. In addition, to regulate gene transcription or protein function, they can also interact with numerous other molecules, including DNA, RNA, proteins and transcription factors [141]. CircRNAs are even able to express small peptides [142]. Finally, they are also involved in epigenetic processes by their interaction with factors associated with DNA methylation and histone modifications [143].

“Further limitations include off-target gene knockdown, side effects of Cas13 expression and toxicity of nanoparticles” [144,145].

Thus, the versatile features and course of actions of circRNAs along with an effective delivery to the cancer target cells aggravate the establishment of targeted therapies with circRNAs. Applying or targeting of circRNAs for therapeutic purposes may not only contribute to tumor suppression but also release oncogenic potential. Thus, numerous shortcomings have to be overcome till circRNAs can enter the clinic.

Finally, the regulation of drug resistance may also occur by other factors, alleviating the effectiveness of circRNAs [8].

10. Conclusion

Due to their role in drug resistance and tumor progression, exosomal and blood derived circRNAs have become a focus of research. As above described, they mainly act as sponges for miRNAs and so can abrogate the function of miRNAs, in oncogenic as well as in tumor suppressive respect. CircRNAs modulate signaling pathways those oncogenic signals activate downstream components that promote tumor progression and reduce the efficacy of drugs resulting drug resistance. Intensive investigations suggest that extracellular circRNAs have the potential to get biomarkers for cancer diagnosis and prognosis, particularly when combined with traditional tumor markers. Dynamic surveillance of the expression levels of oncogenic circRNAs in blood may allow following therapy whether the patients respond to therapy or not.

However, it should be exhorted that circRNAs are involved in a complex regulatory network. Enormous efforts are required to understand how this network contributes to the mechanisms underlying cancer pathogenesis and drug resistance. Apart from circRNAs, a variety of ncRNAs, such as miRNAs, lncRNAs and piRNAs, are involved in this network. Their interaction among each other may revoke the function of the other ncRNAs. Establishment of biological network models in which the interplay of ncRNAs is considered have to be designed, to create specific cancer-associated signatures that permit their application for screening or therapy decisions by the physician.

Different components of multiple signaling pathways may be activated by a circRNAs. Likewise, one signaling pathway can be disturbed by several ncRNAs. The cross-talk between the pathways may elicit oncogenic or tumor suppressive signals, and makes it particularly difficult to precisely define the effectiveness of a treatment using circRNAs as therapeutic agents. Therefore, the consideration of their concentrations in both time and cellular location might facilitate to determine the mode of action of circRNAs. Thus, the development of assays using a circRNAs as therapeutic agents may be laborious to avoid that patients suffer from severe adverse side effects.

In order to effectively target oncogenic circRNAs and to overcome drug resistance the technical platforms tailored to the knockdown of a specific circRNA and the selection of an appropriate delivery system have to be advanced to enable their entry into the clinic. In this respect, exosomes manipulated with specific surface marker for readily finding their target cells presents new possibilities to improve cancer therapy. In addition, increasing evidence have assured the potential clinical application of the measurements of the levels of circRNAs in blood. In this respect, circRNAs may serve as potential diagnostic and prognostic biomarkers to follow treatment course.

Conflicts of interests

The author declares no conflicts of interest.

Reference

[1] Kastan MB, Bartek J. Cell-cycle checkpoints and cancer. *Nature* 2004, 432(7015):316–323.

[2] Potente M, Gerhardt H, Carmeliet P. Basic and therapeutic aspects of angiogenesis. *Cell* 2011, 146(6):873–887.

[3] Jonckheere S, Adams J, De Groote D, Campbell K, Berx G, *et al.* Epithelial-Mesenchymal Transition (EMT) as a Therapeutic Target. *Cells Tissues Org.* 2022, 211(2):157–182.

[4] Rodriguez FJ, Lewis-Tuffin LJ, Anastasiadis PZ. E-cadherin's dark side: Possible role in tumor progression. *Biochim. Biophys. Acta, Rev. Cancer* 2012, 1826(1):23–31.

[5] Géraud C, Koch PS, Damm F, Schledzewski K, Goerdt S. The metastatic cycle: Metastatic niches and cancer cell dissemination. *J. Dtsch. Dermatol.* 2014, 12(11):1012–1019.

[6] Klein CA. Cancer progression and the invisible phase of metastatic colonization. *Nat. Rev. Cancer* 2020, 20(11):681–694.

[7] de Visser KE, Joyce JA. The evolving tumor microenvironment: From cancer initiation to metastatic outgrowth. *Cancer Cell* 2023, 41(3):374–403.

[8] Longley D, Johnston P. Molecular mechanisms of drug resistance. *J. Pathol.* 2005, 205(2):275–292.

[9] Chaplin DD. Overview of the immune response. *J. Allergy Clin. Immun.* 2010, 125(2):S3–S23.

[10] Zhou Y, Tang W, Zhuo H, Zhu D, Rong D, *et al.* Cancer-associated fibroblast exosomes promote chemoresistance to cisplatin in hepatocellular carcinoma through circZFR targeting signal transducers and activators of transcription (STAT3)/ nuclear factor -kappa B (NF-κB) pathway. *Bioengineered* 2022, 13(3):4786–4797.

[11] Tang S, Ning Q, Yang L, Mo Z, Tang S. Mechanisms of immune escape in the cancer immune cycle. *Int. Immunopharmacol.* 2020, 86:106700.

[12] Esteller M. Epigenetics in Cancer. *New Engl. J. Med.* 2008, 358(11):1148–1159.

[13] Ducasse M, Brown MA. Epigenetic aberrations and cancer. *Mol. Cancer* 2005, 5:1–10.

[14] Schwarzenbach H, Gahan PB. Resistance to cis- And carboplatin initiated by epigenetic changes in ovarian cancer patients. *Cancer Drug Resistance* 2019, 2(2):271–296.

[15] Chen L, Shan G. CircRNA in cancer: Fundamental mechanism and clinical potential. *Cancer Lett.* 2021, 505:49–57.

[16] Khan S, Jha A, Panda AC, Dixit A. Cancer-Associated circRNA–miRNA–mRNA Regulatory Networks: A Meta-Analysis. *Front. Mol. Biosci.* 2021, 8:671309.

[17] Zhang F, Jiang J, Qian H, Yan Y, Xu W. Exosomal circRNA: emerging insights into cancer progression and clinical application potential. *J. Hematol. Oncol.* 2023, 16(1):67.

[18] Park EG, Ha H, Lee DH, Kim WR, Lee YJ, *et al.* Genomic Analyses of Non-Coding RNAs Overlapping Transposable Elements and Its Implication to Human Diseases. *Int. J. Mol. Sci.* 2022, 23(16):8950.

[19] Zhang W, He Y, Zhang Y. CircRNA in ocular neovascular diseases: Fundamental mechanism and clinical potential. *Pharmacol. Res.* 2023, 197:106946.

[20] Li J, Zhang G, Liu CG, Xiang X, Le MTN, *et al.* The potential role of exosomal circRNAs in the tumor microenvironment: insights into cancer diagnosis and therapy. *Theranostics* 2022, 12(1):87–104.

[21] Chen J, Gu J, Tang M, Liao Z, Tang R, *et al.* Regulation of cancer progression by circRNA and functional proteins. *J. Cell Physiol.* 2022, 237(1):373–388.

[22] Hansen TB, Jensen TI, Clausen BH, Bramsen JB, Finsen B, *et al.* Natural RNA circles function as efficient microRNA sponges. *Nature* 2013, 495(7441):384–388.

[23] Bartel DP. MicroRNAs: Target Recognition and Regulatory Functions. *Cell* 2009, 136(2):215–233.

[24] Schwarzenbach H. Interplay of microRNAs and circRNAs in Epithelial Ovarian Cancer. *Noncoding RNA* 2024, 10(5):51.

[25] Donati B, Lorenzini E, Ciarrocchi A. BRD4 and Cancer: Going beyond transcriptional regulation. *Mol. Cancer* 2018, 17(1):164.

[26] Li X, Yang L, Chen LL. The Biogenesis, Functions, and Challenges of Circular RNAs. *Mol. Cell* 2018, 71(3):428–442.

[27] Hu Q, Zhou T. EIciRNA-mediated gene expression: tunability and bimodality. *FEBS Lett.* 2018, 592(20):3460–3471.

[28] Mandel P MP. Les acides nucleiques du plasma sanguin chez l' homme [The nucleic acids in blood plasma in humans]. *CR Seances Soc Biol Fil* 1948, 142:241–243.

[29] Crowley E, Di Nicolantonio F, Loupakis F, Bardelli A. Liquid biopsy: monitoring cancer-genetics in the blood. *Nat. Rev. Clin. Oncol.* 2013, 10(8):472–484.

[30] Stroun M, Anker P, Maurice P, Gahan PB. Circulating Nucleic Acids in Higher Organisms. *Int. Rev. Cytol.* 1977, 51:1–48.

[31] Stroun M, Anker P, Lyautey J, Lederrey C, Maurice PA. Isolation and characterization of DNA from the plasma of cancer patients. *Eur. J. Cancer Clin. Oncol.* 1987, 23(6):707–712.

[32] Thierry AR, El Messaoudi S, Gahan PB, Anker P, Stroun M. Origins, structures, and functions of circulating DNA in oncology. *Cancer Metast. Rev.* 2016, 35:347–376.

[33] Rashed MH, Bayraktar E, Helal GK, Abd-Ellah MF, Amero P, *et al.* Exosomes: From garbage bins to promising therapeutic targets. *Int. J. Mol. Sci.* 2017, 18(3):538.

[34] Schwarzenbach H, Gahan P. MicroRNA Shuttle from Cell-To-Cell by Exosomes and Its Impact in Cancer. *Noncoding RNA* 2019, 5(1):28.

[35] Krylova SV., Feng D. The Machinery of Exosomes: Biogenesis, Release, and Uptake. *Int. J. Mol. Sci.* 2023, 24(2):1337.

[36] Van Niel G, Porto-Carreiro I, Simoes S, Raposo G. Exosomes: A common pathway for a specialized function. *J. Biochem.* 2006, 140(1):13–21.

[37] Schwarzenbach H, Gahan PB. Predictive value of exosomes and their cargo in drug response/resistance of breast cancer patients. *Cancer Drug Resistance* 2020, 3(1):63–83.
[38] Li X, Li X, Zhang B, He B. The Role of Cancer Stem Cell-Derived Exosomes in Cancer Progression. *Stem Cells Int.* 2022, 2022(1):9133658.
[39] Chen J, Zhang G, Wan Y, Xia B, Ni Q, *et al.* Immune cell-derived exosomes as promising tools for cancer therapy. *J. Controlled Release* 2023, 364:508–528.
[40] Schwarzenbach H, Gahan PB. Exosomes in immune regulation. *Noncoding RNA* 2021, 7(1):4.
[41] Guo W, Qiao T, Dong B, Li T, Liu Q, *et al.* The Effect of Hypoxia-Induced Exosomes on Anti-Tumor Immunity and Its Implication for Immunotherapy. *Front Immunol.* 2022, 13:915985.
[42] Liu Y, Li X, Zhang T, Liu G. The Roles of Exosomes in Ovarian Cancer Chemo-resistance. *J. Cancer* 2023, 14(11):2128–2144.
[43] Chen C, Ma Z, Jiang H. EMT Participates in the Regulation of Exosomes Secretion and Function in Esophageal Cancer Cells. *Technol. Cancer Res. Treat.* 2021, 20: 15330338211033077.
[44] Han QF, Li WJ, Hu KS, Gao J, Zhai WL, *et al.* Exosome biogenesis: machinery, regulation, and therapeutic implications in cancer. *Mol. Cancer* 2022, 21(1):207.
[45] Nigam SK. What do drug transporters really do? *Nat. Rev. Drug Discov.* 2015, 14(1):29–44.
[46] Vasiliou V, Vasiliou K, Nebert DW. Human ATP-binding cassette (ABC) transporter family. *Hum. Genomics* 2008, 3:281.
[47] Hrabeta J, Adam V, Eckschlager T, Frei E, Stiborova M, *et al* Metal Containing Cytostatics and Their Interaction with Cellular Thiol Compounds Causing Chemoresistance. *Anticancer Agents Med. Chem.* 2016, 16(6):686–698.
[48] Nyce J. Drug-induced DNA Hypermethylation and Drug Resistance in Human Tumors. *Cancer Res.* 1989, 49(21): 5829–5836.
[49] Zhou J, Kang Y, Chen L, Wang H, Liu J, *et al.* The Drug-Resistance Mechanisms of Five Platinum-Based Antitumor Agents. *Front Pharmacol.* 2020, 11:343.
[50] Picard M. Management of Hypersensitivity Reactions to Taxanes. *Immunol. Allergy Clin. North. Am.* 2017, 37(4):679–693.
[51] Meredith AM, Dass CR. Increasing role of the cancer chemotherapeutic doxorubicin in cellular metabolism. *J. Pharm. Pharmacol.* 2016, 68(6):729–741.
[52] Li X, Li M, Huang M, Lin Q, Fang Q, *et al.* The multi-molecular mechanisms of tumor-targeted drug resistance in precision medicine. *Biomed. Pharmacother.* 2022, 150:13064.
[53] Sharpe AH, Pauken KE. The diverse functions of the PD1 inhibitory pathway. *Nat. Rev. Immunol.* 2018;18(3):153–167.
[54] Chen MK, Liang ZJ, Luo DS, Xue KY, Liao DY, *et al.* Abiraterone, Orteronel, Enzalutamide and Docetaxel: Sequential or Combined Therapy? *Front Pharmacol.* 2022, 13:843110.

[55] Wu YL, Zhou C, Liam CK, Wu G, Liu X, *et al.* First-line erlotinib *versus* gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study. *Ann. Oncol.* 2015, 26(9):1883–1889.

[56] Tomar MS, Kumar A, Srivastava C, Shrivastava A. Elucidating the mechanisms of Temozolomide resistance in gliomas and the strategies to overcome the resistance. *Biochim. Biophys. Acta Rev. Cancer* 2021, 1876(2):188616.

[57] Tan CRC, Abdul-Majeed S, Cael B, Barta SK. Clinical Pharmacokinetics and Pharmacodynamics of Bortezomib. *Clin. Pharmacokinet.* 2018:157–168.

[58] Ebrahimi N, Fardi E, Ghaderi H, Palizdar S, Khorram R, Vafadar R, *et al.* Receptor tyrosine kinase inhibitors in cancer. *Cell. Mol. Life Sci.* 2023, 80(4):104.

[59] Xue C, Li G, Lu J, Li L. Crosstalk between circRNAs and the PI3K/AKT signaling pathway in cancer progression. *Signal Transduct Target Ther.* 2021, 6(1):400.

[60] Xue C, Li G, Zheng Q, Gu X, Bao Z, *et al.* The functional roles of the circRNA/Wnt axis in cancer. *Mol. Cancer* 2022, 21(1):108.

[61] Farooqi AA, Naureen H, Attar R. Regulation of cell signaling pathways by circular RNAs and microRNAs in different cancers: Spotlight on Wnt/β-catenin, JAK/STAT, TGF/SMAD, SHH/GLI, NOTCH and Hippo pathways. *Semin. Cell. Dev. Biol.* 2022, 124:72–81.

[62] Fruman DA, Chiu H, Hopkins BD, Bagrodia S, Cantley LC, *et al.* The PI3K Pathway in Human Disease. *Cell* 2017, 170(4):605–635.

[63] Carnero A, Blanco-Aparicio C, Renner O, Link W, Leal J. The PTEN/PI3K/AKT Signalling Pathway in Cancer, Therapeutic Implications. *Curr. Cancer Drug Targets* 2008, 8(3):187–198.

[64] Paplomata E, O'Regan R. The PI3K/AKT/mTOR pathway in breast cancer: targets, trials and biomarkers. *Ther. Adv. Med. Oncol.* 2014, 6(4):154–166.

[65] Wang L, Yang X, Zhou F, Sun X, Li S. Circular RNA UBAP2 facilitates the cisplatin resistance of triple-negative breast cancer via microRNA-300/anti-silencing function 1B histone chaperone/PI3K/AKT/mTOR axis. *Bioengineered* 2022, 13(3):7197–7208.

[66] Li H, Xu W, Xia Z, Liu W, Pan G, *et al.* Hsa_circ_0000199 facilitates chemo-tolerance of triple-negative breast cancer by interfering with miR-206/613-led PI3K/Akt/mTOR signaling. *Aging* 2021, 13(3):4522–4551.

[67] Nusse R, Clevers H. Wnt/β-Catenin Signaling, Disease, and Emerging Therapeutic Modalities. *Cell* 2017, 169(6):985–999.

[68] Wu CI, Hoffman JA, Shy BR, Ford EM, Fuchs E *et al.* Function of Wnt/β-catenin in counteracting Tcf3 repression through the Tcf3–β-catenin interaction. *Development* 2012, 139(12):2118–2129.

[69] Ying Y, Tao Q. Epigenetic disruption of the WNT/ß-catenin signaling pathway in human cancers. *Epigenetics* 2009, 4(5):307–312.

[70] MacDonald BT, Tamai K, He X. Wnt/beta-catenin signaling: components, mechanisms, and diseases. *Dev. Cell* 17(1): 9–26.

[71] Li J, Ma J, Huang S, Li J, Zhou L, *et al.* CircTTLL13 Promotes TMZ Resistance in Glioma via Modulating OLR1-Mediated Activation of the Wnt/β-Catenin Pathway. *Mol. Cell Biol.* 2023, 43(7):354–369.

[72] Zhou Q, Fu Q, Shaya M, Kugeluke Y, Li S, *et al.* Knockdown of circ_0055412 promotes cisplatin sensitivity of glioma cells through modulation of CAPG and Wnt/β-catenin signaling pathway. *CNS Neurosci. Ther.* 2022, 28(6):884–896.

[73] Dong L, Qu F. CircUBAP2 promotes SEMA6D expression to enhance the cisplatin resistance in osteosarcoma through sponging miR-506-3p by activating Wnt/β-catenin signaling pathway. *J. Mol. Histol.* 2020, 51(4):329–340.

[74] Hu X, li J, Fu M, Zhao X, Wang W. The JAK/STAT signaling pathway: from bench to clinic. *Signal Transduct. Target. Ther.* 2021, 6(1):402.

[75] Wang S, Cheng L, Wu H, Li G. Mechanisms and prospects of circular RNAs and their interacting signaling pathways in colorectal cancer. *Front. Oncol.* 2022, 12:949656.

[76] Brzozowa-Zasada M, Piecuch A, Michalski M, Segiet O, Kurek J, *et al.* Notch and its oncogenic activity in human malignancies. *Eur. Surg.* 2017, 49:199–209.

[77] Yao Y, Li X, Cheng L, Wu X, Wu B. Circular RNA FAT atypical cadherin 1 (circFAT1)/microRNA-525-5p/spindle and kinetochore-associated complex subunit 1 (SKA1) axis regulates oxaliplatin resistance in breast cancer by activating the notch and Wnt signaling pathway. *Bioengineered* 2021, 12(1):4032–4043.

[78] Calzado M, Bacher S, Schmitz ML. NF-κB Inhibitors for the Treatment of Inflammatory Diseases and Cancer. *Curr. Med. Chem.* 2007, 14(3):367–376.

[79] Ge L, Sun Y, Shi Y, Liu G, Teng F, *et al.* Plasma circRNA microarray profiling identifies novel circRNA biomarkers for the diagnosis of ovarian cancer. *J. Ovarian Res.* 2022, 15(1):58.

[80] Zhong AN, Yin Y, Tang BJ, Chen L, Shen HW, *et al.* CircRNA Microarray Profiling Reveals hsa_circ_0058493 as a Novel Biomarker for Imatinib-Resistant CML. *Front. Pharmacol.* 2021, 12:728916.

[81] Shao N, Song L, Sun X. Exosomal circ_PIP5K1A regulates the progression of non-small cell lung cancer and cisplatin sensitivity by miR-101/ABCC1 axis. *Mol. Cell. Biochem.* 2021, 476(6):2253–2267.

[82] Wang X, Wang H, Jiang H, Qiao L, Guo C. Circular RNAcirc_0076305 Promotes Cisplatin (DDP) Resistance of Non-Small Cell Lung Cancer Cells by Regulating ABCC1 Through miR-186-5p. *Cancer Biother. Radiopharm.* 2023, 38(5):293–304.

[83] Kun-Peng Z, Xiao-Long M, Chun-Lin Z. Overexpressed circPVT1, a potential new circular RNA biomarker, contributes to doxorubicin and cisplatin resistance of osteosarcoma cells by regulating ABCB1. *Int. J. Biol. Sci.* 2018, 14(3):321–330.

[84] Kunická T, Souček P. Importance of ABCC1 for cancer therapy and prognosis. *Drug Metab. Rev.* 2014, 46(3):325–342.

[85] Zhang Y, Tan X, Lu Y. Exosomal transfer of circ_0006174 contributes to the chemoresistance of doxorubicin in colorectal cancer by depending on the miR-1205/CCND2 axis. *J. Physiol. Biochem.* 2022, 78(1):39–50.

[86] Saleban M, Harris EL, Poulter JA. D-Type Cyclins in Development and Disease. *Genes* 2023, 14(7):1445.

[87] Chen Y, Liu H, Zou J, Cao G, Li Y, *et al.* Exosomal circ_0091741 promotes gastric cancer cell autophagy and chemoresistance via the miR-330-3p/TRIM14/Dvl2/Wnt/β-catenin axis. *Hum. Cell* 2023, 36:258–275.

[88] Deng Y, Zhu H, Xiao L, Liu C, Meng X. Circ_0005198 Enhances Temozolomide Resistance of Glioma Cells Through Mir-198/Trim14 Axis. *Aging* 2021, 13(2):2198–2211.

[89] Xia W, Chen W, Ni C, Meng X, Wu J, *et al.* Chemotherapy-induced exosomal circBACH1 promotes breast cancer resistance and stemness via miR-217/G3BP2 signaling pathway. *Breast Cancer Res.* 2023, 25(1):85.

[90] Wu Y, Xu M, Feng Z, Wu H, Wu J, *et al.* AUF1-induced circular RNA hsa_circ_0010467 promotes platinum resistance of ovarian cancer through miR-637/LIF/STAT3 axis. *Cell. Mol. Life Sci.* 2023, 80(9):256.

[91] Zang R, Qiu X, Song Y, Wang Y. Exosomes Mediated Transfer of Circ_0000337 Contributes to Cisplatin (CDDP) Resistance of Esophageal Cancer by Regulating JAK2 via miR-377-3p. *Front. Cell Dev. Biol.* 2021, 9:673237.

[92] Ding J, Zhang X, Xue J, Fang L, Ban C, *et al.* CircNPM1 strengthens Adriamycin resistance in acute myeloid leukemia by mediating the miR-345-5p/FZD5 pathway. *Cent. Eur. J. Immunol.* 2021, 46:162–182.

[93] Xie H, Yao J, Wang Y, Ni B. Exosome-transmitted circVMP1 facilitates the progression and cisplatin resistance of non-small cell lung cancer by targeting miR-524-5p-METTL3/SOX2 axis. *Drug Deliv.* 2022, 29:1257–1271.

[94] Shi Q, Ji T, Ma Z, Tan Q, Liang J. Serum Exosomes-Based Biomarker circ_0008928 Regulates Cisplatin Sensitivity, Tumor Progression, and Glycolysis Metabolism by miR-488/HK2 Axis in Cisplatin-Resistant Nonsmall Cell Lung Carcinoma. *Cancer Biother. Radiopharm.* 2023, 38(8):558–571.

[95] Liu ZH, Yang SZ, Chen XT, Shao MR, Dong SY, *et al.* Correlations of hsa_circ_0046264 expression with onset, pathological stage and chemotherapy resistance of lung cancer. *Eur. Rev. Med. Pharmacol. Sci.* 2020, 24(18):9511–9521.

[96] Wang C, Xia S. Serum Hsa_circ_0005962 Is A Prognostic Biomarker of Paclitaxel Resistance in Nonsmall Cell Lung Cancer Treatment. *Int. J. Clin. Pract.* 2023, 2023(1):6644168.

[97] Chen SW, Zhu SQ, Pei X, Qiu BQ, Xiong D, *et al.* Cancer cell-derived exosomal circUSP7 induces CD8+ T cell dysfunction and anti-PD1 resistance by regulating the miR-934/SHP2 axis in NSCLC. *Mol. Cancer* 2021, 20:144.

[98] Yang B, Teng F, Chang L, Wang J, Liu DL, *et al.* Tumor-derived exosomal circRNA_102481 contributes to EGFR-TKIs resistance via the miR-30a-5p/ROR1 axis in non-small cell lung cancer. *Aging* 2021, 13(9):13264–13286.

[99] Zhang JW, Xu GY, Wang XF, Zhao YL, Kong QR. Circrna (Circ_0008057) promotes uremic serum-mediated proliferation and migration of vascular smooth muscle cells via mir-370/plk1 signaling pathway. *J. Biol. Regul. Homeost. Agents* 2021, 35(4).

[100] Chao F, Zhang Y, Lv L, Wei Y, Dou X, *et al.* Extracellular Vesicles Derived circSH3PXD2A Inhibits Chemoresistance of Small Cell Lung Cancer by miR-375-3p/YAP1. *Int. J. Nanomedicine* 2023, 18:2989–3006.

[101] Zhang Y, Chao F, Lv L, Li M, Shen Z. Hsa_circ_0041150 serves as a novel biomarker for monitoring chemotherapy resistance in small cell lung cancer patients treated with a first-line chemotherapy regimen. *J. Cancer Res. Clin. Oncol.* 2023, 149(17):15365–15382.

[102] Zou J, Lan H, Li W, Xie S, Tong Z, *et al.* Comprehensive Analysis of Circular RNA Expression Profiles in Gefitinib-Resistant Lung Adenocarcinoma Patients. *Technol. Cancer Res. Treat.* 2022, 21:15330338221139167.

[103] Li J, Zhu T, Weng Y, Cheng F, Sun Q, et al. Exosomal circDNER enhances paclitaxel resistance and tumorigenicity of lung cancer via targeting miR-139-5p/ITGB8. *Thorac. Cancer* 2022, 13(9):1381–1390.

[104] Gao J, Ao YQ, Zhang LX, Deng J, Wang S, *et al.* Exosomal circZNF451 restrains anti-PD1 treatment in lung adenocarcinoma via polarizing macrophages by complexing with TRIM56 and FXR1. *J. Exp. Clin. Canc. Res.* 2022, 41(1):295.

[105] Hon KW, Ab-Mutalib NS, Abdullah NMA, Jamal R, Abu N. Extracellular Vesicle-derived circular RNAs confers chemoresistance in Colorectal cancer. *Sci. Rep.* 2019, 9(1):16497.

[106] Hui B, Zhou C, Xu Y, Wang R, Dong Y, *et al.* Exosomes secreted by Fusobacterium nucleatum-infected colon cancer cells transmit resistance to oxaliplatin and 5-FU by delivering hsa_circ_0004085. *J. Nanobiotechnology* 2024, 22(1):62.

[107] Pan Z, Zheng J, Zhang J, Lin J, Lai J, *et al.* A Novel Protein Encoded by Exosomal CircATG4B Induces Oxaliplatin Resistance in Colorectal Cancer by Promoting Autophagy. *Adv. Sci.* 2022, 9(35):e2204513.

[108] Wang X, Zhang H, Yang H, Bai M, Ning T, *et al.* Exosome-delivered circRNA promotes glycolysis to induce chemoresistance through the miR-122-PKM2 axis in colorectal cancer. *Mol. Oncol.* 2020, 14(3):539–555.

[109] Yang G, Tan J, Guo J, Wu Z, Zhan Q. Exosome-mediated transfer of circ_0063526 enhances cisplatin resistance in gastric cancer cells via regulating miR-449a/SHMT2 axis. *Anticancer Drug.* 2022, 33(10):1047–1057.

[110] Yao W, Guo P, Mu Q, Wang Y. Exosome-Derived Circ-PVT1 Contributes to Cisplatin Resistance by Regulating Autophagy, Invasion, and Apoptosis Via miR-30a-5p/YAP1 Axis in Gastric Cancer Cells. *Cancer Biother. Radiopharm.* 2021, 36(4):347–359.

[111] Liang Q, Chu F, Zhang L, Jiang Y, Li L, *et al.* circ-LDLRAD3 Knockdown Reduces Cisplatin Chemoresistance and Inhibits the Development of Gastric Cancer with Cisplatin Resistance through miR-588 Enrichment-Mediated SOX5 Inhibition. *Gut Liver* 2023, 17(3):389–403.

[112] Zang X, Wang R, Wang Z, Qiu S, Zhang F, *et al.* Exosomal circ50547 as a potential marker and promotor of gastric cancer progression via miR-217/HNF1B axis. *Transl. Oncol.* 2024, 45:101969.

[113] Zhong Y, Wang D, Ding Y, Tian G, Jiang B. Circular RNA circ_0032821 contributes to oxaliplatin (OXA) resistance of gastric cancer cells by regulating SOX9 via miR-515-5p. *Biotechnol. Lett.* 2021, 43:339–351.

[114] Geng X, Zhang Y, Lin X, Zeng Z, Hu J, *et al.* Exosomal circWDR62 promotes temozolomide resistance and malignant progression through regulation of the miR-370-3p/MGMT axis in glioma. *Cell Death Dis.* 2022, 13(7):596.

[115] Li X, Wang N, Leng H, Yuan H, Xu L. Hsa_circ_0043949 reinforces temozolomide resistance via upregulating oncogene ITGA1 axis in glioblastoma. *Metab. Brain Dis.* 2022, 37(8):2979–2993.

[116] Han C, Wang S, Wang H, Zhang J. Exosomal circ-HIPK3 Facilitates Tumor Progression and Temozolomide Resistance by Regulating miR-421/ZIC5 Axis in Glioma. *Cancer Biother. Radiopharm.* 2021, 36(7):537–548.

[117] Si J, Li W, Li X, Cao L, Chen Z, *et al.* Heparanase confers temozolomide resistance by regulation of exosome secretion and circular RNA composition in glioma. *Cancer Sci.* 2021, 112(9):3491–3506.

[118] Tan WQ, Yuan L, Wu XY, He CG, Zhu SC, *et al.* Exosome-delivered circular RNA DLGAP4 induces chemoresistance via miR-143-HK2 axis in neuroblastoma. *Cancer Biomarkers* 2022, 34(3):375–384.

[119] Zhang PF, Gao C, Huang XY, Lu JC, Guo XJ, *et al.* Cancer cell-derived exosomal circUHRF1 induces natural killer cell exhaustion and may cause resistance to anti-PD1 therapy in hepatocellular carcinoma. *Mol. Cancer* 2020, 19:1–15.

[120] Zhang L, Xu T, Li Y, Pang Q, Ding X. Serum hsa_circ_0000615 is a prognostic biomarker of sorafenib resistance in hepatocellular carcinoma. *J. Clin. Lab. Anal.* 2022, 36(11):e24741.

[121] Lim MCJ, Baird AM, Greene J, McNevin C, Ronan K, *et al.* Hsa_circ_0001275 is one of a number of circRNAs dysregulated in enzalutamide resistant prostate cancer and confers enzalutamide resistance *in vitro*. *Cancers* 2021, 13(24):6383.

[122] Tan X, Song X, Fan B, Li M, Zhang A, *et al.* Exosomal circRNA Scm-like with four malignant brain tumor domains 2 (circ-SFMBT2) enhances the docetaxel resistance of prostate cancer via the microRNA-136-5p/tribbles homolog 1 pathway. *Anticancer Drug.* 2022, 33(9):871–882.

[123] Tao W, Luo ZH, He Y Di, Wang BY, Xia TL, *et al.* Plasma extracellular vesicle circRNA signature and resistance to abiraterone in metastatic castration-resistant prostate cancer. *Br. J. Cancer* 2023, 128(7):1320–1332.

[124] Zeng Z, Zhao Y, Chen QY, Zhu S, Niu Y, *et al.* Hypoxic exosomal HIF-1α-stabilizing circZNF91 promotes chemoresistance of normoxic pancreatic cancer cells via enhancing glycolysis. *Oncogene* 2021, 40(36):5505–5517.

[125] Pan Y, Lin Y, Mi C. Cisplatin-resistant osteosarcoma cell-derived exosomes confer cisplatin resistance to recipient cells in an exosomal circ_103801-dependent manner. *Cell Biol. Int.* 2021, 45(4):858–868.

[126] Wu X, Ren Y, Yao R, Zhou L, Fan R. Circular RNA circ-MMP11 Contributes to Lapatinib Resistance of Breast Cancer Cells by Regulating the miR-153-3p/ANLN Axis. *Front. Oncol.* 2021, 11:639961.

[127] Chen J, Wu S, Wang J, Sha Y, Ji Y. Hsa_circ_0074269-mediated Upregulation of TUFT1 Through miR-485-5p Increases Cisplatin Resistance in Cervical Cancer. *Reprod. Sci.* 2022, 29(8):2236–2250.

[128] Lin J, Qin H, Han Y, Li X, Zhao Y, *et al.* Circnrip1 modulates the mir-515-5p/il-25 axis to control 5-fu and cisplatin resistance in nasopharyngeal carcinoma. *Drug Des. Devel. Ther.* 2021, 15:323–330.

[129] Louis C, Ferlier T, Leroux R, Pineau R, Desoteux M, *et al.* TGFβ-induced circLTBP2 predicts a poor prognosis in intrahepatic cholangiocarcinoma and mediates gemcitabine resistance by sponging miR-338-3p. *JHEP Reports* 2023, 5(12):100900.

[130] Wang X, Cheng Q. Suppression of exosomal hsa_circ_0001005 eliminates the Vemurafenib resistance of melanoma. *J. Cancer Res. Clin. Oncol.* 2023, 149(9):5921–5936.

[131] Luo Y, Gui R. Circulating exosomal circmyc is associated with recurrence and bortezomib resistance in patients with multiple myeloma. *Turk. J. Hematol.* 2020, 37(4):248–262.

[132] Cao H xia, Miao C feng, Sang L na, Huang Y min, Zhang R, *et al.* Circ_0009910 promotes imatinib resistance through ULK1-induced autophagy by sponging miR-34a-5p in chronic myeloid leukemia. *Life Sci.* 2020, 243:117255.

[133] Solé C, Mentxaka G, Lawrie CH. The Use of circRNAs as Biomarkers of Cancer. *Methods Mol. Biol.* 2021, 2348:307–341.

[134] He AT, Liu J, Li F, Yang BB. Targeting circular RNAs as a therapeutic approach: current strategies and challenges. *Signal Transduct. Target. Ther.* 2021, 6(1):185.

[135] Schwarzenbach H. Potential of Exosomes as Therapeutics and Therapy Targets in Cancer Patients. *Int. J. Transl. Med.* 2024, 4(2):247–261.

[136] Hwang DW, Choi H, Jang SC, Yoo MY, Park JY, *et al.* Noninvasive imaging of radiolabeled exosome-mimetic nanovesicle using 99mTc-HMPAO. *Sci. Rep.* 2015, 5(1):15636.

[137] Munagala R, Aqil F, Jeyabalan J, Kandimalla R, Wallen M, *et al.* Exosome-mediated delivery of RNA and DNA for gene therapy. *Cancer Lett.* 2021, 505:58–72.

[138] Yang Z, Xie J, Zhu J, Kang C, Chiang C, *et al.* Functional exosome-mimic for delivery of siRNA to cancer: in vitro and in vivo evaluation. *J. Controlled Release* 2016, 505:243.

[139] Choi Y, Yu A-M. ABC Transporters in Multidrug Resistance and Pharmacokinetics, and Strategies for Drug Development. *Curr. Pharm. Des.* 2014, 20(5):793–807.

[140] Liu Z, Dai Q, Yu X, Duan X, Wang C. Predicting circRNA-drug resistance associations based on a multimodal graph representation learning framework. *IEEE J. Biomed. Health Inform.* 2023, 1–11.

[141] Chen LL. The expanding regulatory mechanisms and cellular functions of circular RNAs. *Nat. Rev. Mol. Cell Biol.* 2020, 21(8):475–490.

[142] Wu P, Mo Y, Peng M, Tang T, Zhong Y, *et al.* Emerging role of tumor-related functional peptides encoded by lncRNA and circRNA. *Mol. Cancer* 2020, 19:1–14.

[143] Xu T, Wang L, Jia P, Song X, Zhao Z. An integrative transcriptomic and methylation approach for identifying differentially expressed circular rnas associated with dna methylation change. *Biomedicines* 2021, 9(6):657.

[144] Li S, Li X, Xue W, Zhang L, Yang LZ, *et al.* Screening for functional circular RNAs using the CRISPR–Cas13 system. *Nat. Methods* 2021, 18(1):51–59.

[145] Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, *et al.* Engineering precision nanoparticles for drug delivery. *Nat. Rev. Drug Discov.* 2021, 20(2):101–124.