Presence and prospects of exosomal circRNAs in cancer (Review)

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Received September 15, 2022; Accepted December 20, 2022

DOI: 10.3892/ijo.2023.5495

Abstract. Exosomes are nanoscale extracellular vesicles secreted by parent cells and they are present in most bodily fluids, are able to carry active substances through intercellular transport and mediate communication between different cells, in particular those active in cancer. Circular RNAs (circRNAs) are novel noncoding RNAs expressed in most eukaryotic cells and are involved in various physiological and pathological processes, particularly in the occurrence and progression of cancer. Numerous studies have indicated a close relationship between circRNAs and exosomes. Exosomal circRNAs (exo-circRNAs) are a type of circRNA enriched in exosomes that may participate in the progression of cancer. Based on this, exo-circRNAs may have an important role in malignant behavioral manifestations of cancer and hold great promise in the diagnosis and treatment of cancer. The present review gives an introduction to the origin and functions of exosomes and circRNAs and elaborates on the mechanisms of exo-circRNAs in cancer progression. The biological functions of exo-circRNAs in tumorigenesis, development and drug resistance, as well as their role as predictive biomarkers, were discussed.

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Abbreviations: ILVs, intraluminal vesicles; ESCRT, endosomal sorting complex required for transport; MVBs, multivesicular bodies; COP, coat protein complex; EMT, epithelial-mesenchymal transition; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer; MM, multiple myeloma; miRNAs, microRNAs; circRNAs, circular RNAs; ecircRNA, exonic circRNAs; ciRNAs, intronic circRNAs; EIciRNAs, exonic-intronic circRNAs; ORF, open reading frame; IRES, internal ribosome entry site; m6A, N6-methyladenosines; ICBPS, internal complementary base pair sequences; HCC, hepatocellular carcinoma; PDAC, pancreatic ductal adenocarcinoma; HUVECs, human umbilical vein endothelial cells; UCB, urothelial carcinoma of the bladder; FSCN1, fascin actin-bundling protein 1; VEGF, vascular endothelial growth factor; TGF-β1, transforming growth factor-β1; circARHGAP10, circRNA Rho GTPase activating protein 10; PKM2, pyruvate kinase isoenzyme 2; DDP, cisplatin; SCAI, suppressor of cancer cell invasion; TMZ, temozolomide; GLUT1, glucose transporter 1; HK2, hexokinase-2; HGA, high-grade astrocytoma; WAT, white adipose tissue

Key words: exosome, circRNA, exo-circRNAs, cancer

Contents

1. Introduction

Exosomes are a special class of nanoscale vesicles that are secreted by most eukaryotic cells and exist extensively in the extracellular space (1). Exosomes may be found in a variety of body fluids, such as blood, urine and saliva, and may carry a variety of molecules, such as RNAs, DNAs, proteins and lipids (2). These are transported to the appropriate cell and affect their biological function. Therefore, exosomes are known as carriers of intercellular information transfer. This is important for tumor progression (3).

Circular RNAs (circRNAs) are a class of noncoding RNAs that widely exist in eukaryotic cells (4). They have specific biological functions by regulating microRNA (miRNA) and proteins (5) and are closely related to the occurrence, development and prognosis of various malignant tumors. Their functions include acting as miRNA sponges (6), interactions with RNA-binding proteins (7) and translating proteins (8). Clinical studies have indicated that certain circRNAs are significantly different in terms of their expression between normal individuals and patients with cancer, which means that circRNAs are expected to be new diagnostic markers for cancer (9,10).

Studies have indicated that certain circRNAs are enriched and highly expressed in exosomes, participate in extracellular transport and are finally released into target cells, regulating the biological behavior of target cells (11). These circRNAs that are loaded and transported by exosomes are called exosomal circRNAs (exo-circRNAs). Based on the characteristics of exosomes and circRNAs, exo-circRNAs may have a more unique role in cancer progression. In the present review, the origins and functions of exosomes and circRNAs were briefly summarized and recent advances in the molecular mechanisms of exo-circRNAs in cancer growth, metastasis and drug resistance were highlighted. Exo-circRNAs are expected to be potential neoteric cancer prediction markers and therapeutic targets.

2. Generation and function of exosomes and circRNAs

Biogenesis and functions of exosomes. Exosomes (30-100 nm in diameter) are extracellular vesicles that were first identified in 1987 (12). Other extracellular vesicles also include microbubbles (50-2,000 nm in diameter), which are produced by the plasma membrane to germinate and some of them are always rich in certain proteins (13), reverse transcription virus-like particles (90-100 nm in diameter), directly by the plasma membrane of germination, containing an endogenous retrovirus sequence (14) and apoptotic bodies (500-4,000 nm in diameter, programmed cell death of package cell residue vesicles (15,16). Unlike these, exosomes originate from small vesicles formed by the endocytosis of cell membranes (17). When the surface of the cell membrane is rich in clathrin, it is easy to induce the inward budding of the cell membrane to form endocytic vesicles (18). In addition, specific lipid rafts on the cell membrane may also induce endocytosis, which is the source of the early endosome (Fig. 1) (19). Early endosomes may mediate the inward transfer of numerous substances from the cytoplasm to the endosome, which is similar to cargo shipment (20). With the assistance of the Golgi body, the endoplasmic membrane spits inward and certain substances in the cytoplasm are injected into it to form intraluminal vesicles (ILVs) (21). Early endosomes are thus transformed into late endosomes, also known as multivesicular bodies, due to their abundance of ILVs (22). ILVs are the prototype of exosomes (23). The most discussed molecular mechanism is the endosomal sorting complex required for transport (ESCRT) (24). ESCRT is composed of four complexes (named ESCRT-0, I, II and III) and related assistant proteins. Of these proteins, ESCRT-0 recruits cargo in a ubiquitin-dependent manner, mainly as ubiquitin proteins (25). ESCRT-I and ESCRT-II may induce the inner body membrane to germinate inward and the helper protein apoptosis-linked gene-2 interacting protein X is also involved (24,26). ESCRT-III drives vesicles to be released from the membrane and the auxiliary protein VPS4 is able to assist ATP-dependent reactions to induce the dissociation of activated ESCRT complexes and promote their recovery (27). In addition, there have been reports of non-ESCRT-dependent shipments. For instance, miRNA may be loaded in lipid rafts rich in ceramide on the endosomal membrane (19). In addition, studies including that by Odorizzi *et al* (28) found that in the early endosomal membrane of yeast cells, there are specific regions called tetraspanin-enriched microdomains, which consist of four transmembrane domains that form a stereotypic tertiary structure and may interact with specific proteins in the cytoplasm to promote ILV formation (Fig. 1) (29). Multivesicular bodies (MVBs) experience two outcomes. One is that lysosomes conjugate and degrade their lumen, which is the reason why exosomes were initially known as garbage collectors (30). It may be that activating conjugation of ISG15 by ubiquitin-like protein prevents the release of exosomes and facilitates the fusion of MVBs and lysosomes (31). Second, MVBs fuse with the cell membrane, releasing ILVs into the extracellular space and fluid circulation. These are called exosomes. This requires the assistance of a variety of molecules, including coat protein complex (COP) I and II, soluble NSF attachment protein receptors (SNARE) and Rab GTPases (32). Among them, COP I and II mainly mediate vesicle transport (33,34). The Rab GTPase family is responsible for transporting MVBs to the cell membrane, inducing vesicle budding, vesicle and organelle mobility through cytoskeletal interactions and docking of vesicles to their target compartment, leading to membrane fusion (23,35). For instance, Rab35 mediates the docking of MVBs in nerve cells with cell membranes (36). SNARE is a membrane protein family and the SNARE in the transport vesicle (known as v-SNARE) is paired with its corresponding SNARE binding partner (known as t-SNARE), mediating the fusion of MVBs and the cell membrane (Fig. 1) (32,37). Next, circulating exosomes search for specific receptor cells and are internalized by receptor cells by phagocytosis, pinocytosis or fusion with the cell membrane, possibly with the help of specific mediators such as integrins, lipids, lectins and adhesion. Hoshino *et al* (38) found that exosome integrins $\alpha6\beta4$ and $\alpha6\beta1$ were associated with lung metastasis.

Roles of exosomes in cancer. It is worth noting that exosomes not only have an important role in regulating normal physiological functions, such as tissue regeneration (39), immune surveillance, blood circulation (40) and stem cell plasticity. A large number of studies have indicated that exosomes in tumors also have an important role in regulating cell proliferation, metastasis and drug resistance, and as biomarkers (41,42). Exosomes derived from cancer cells are deemed important drivers of pre-metastatic niche formation at distant organs, such as the secreted ADAM17 transported via exosomes, which was indicated to promote the migratory ability of colorectal cancer (CRC) cells by cleaving the E-cadherin junction (42). Epithelial-mesenchymal transition (EMT) is a process in which epithelial cells acquire mesenchymal features. In cancer, EMT is associated with tumor initiation, invasion, metastasis and resistance to therapy (43). Exosomes secreted by cancer-associated fibroblasts in CRC enhance EMT of CRC cells, thereby promoting CRC metastasis and drug resistance (44). Exosomes may affect recipient cells through the engulfed cargos and exosomes have already emerged as important mediators for intercellular communication (45). Osimertinib is a third-generation epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) approved for the treatment of patients with EGFR-mutant non-small cell lung cancer (NSCLC). Current research indicated that exosomal miR-210-3p may have a crucial role in resistance to osimertinib in the tumor microenvironment of

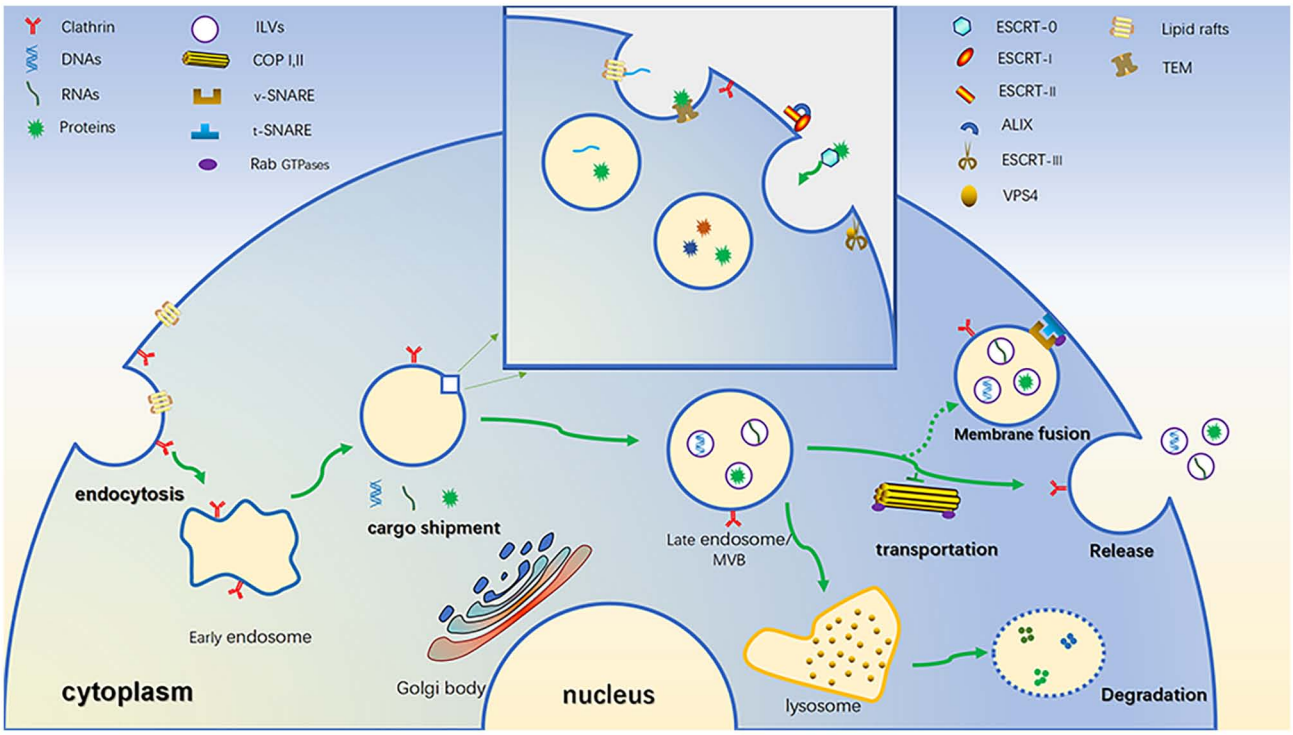

Figure 1. Biogenesis of exosomes. i) Endocytosis: Cell membranes rich in clathrin and lipid raft microregions germinate inward and form early endosomes; ii) cargo sorting: Early endosomes are able to recruit DNAs, RNAs, proteins and other molecules, which are wrapped by endosome membrane and transferred into early endosomes, forming ILVs. Early endosomes become late endosomes, also known as MVBs; iii) Transport and release: MVBs are able to actively move to the cell membrane, fuse with the cell membrane, release ILVs to extracellular matrix, which are called exosomes. In addition, MVBs may be recognized by lysosomes and degrade their cargo. ILVs, intraluminal vesicles; COP, coat protein complex; SNARE, soluble NSF attachment protein receptors; ESCRT, endosomal sorting complex required for transport; ALIX, apoptosis-linked gene-2 interacting protein X; VPS4, vacuolar protein sorting protein 4; TEM, tetraspanin-enriched microdomains.

EGFR-mutant NSCLC (46). In breast cancer cells, extracellular long noncoding RNA small nucleolar RNA host gene 14 was able to be incorporated into exosomes and transmitted to sensitive cells, thus disseminating trastuzumab resistance (47). Therefore, exosomes may have an important role in drug resistance by influencing the tumor microenvironment and non-coding RNA. Cancer-secreted exosomes have an effect on the exosome donor cells and support cancer growth and metastasis (48). In multiple myeloma (MM), exosomes derived from mesenchymal stromal cells promote the progression of MM via LINCI00461 (49). Furthermore, breast cancer exosomes have been indicated to promote cell proliferation and cancer progression (50). Given that exosomes have an important role in all aspects of tumors, exosomes may be used as biomarkers to predict cancer progression in advance and may have applications in tumor diagnosis, anti-tumor chemotherapy and drug resistance prediction (51-53). Exosomal miRNAs have been indicated to be highly sensitive and specific in distinguishing healthy individuals from patients with CRC (54). Exosome enrichment may be found in the serum of patients with cisplatin-resistant gastric cancer (GC) and the results suggest that exosomes derived from drug-resistant cells may serve as a potential predictor of the response to antitumor chemotherapy (53).

Generation and function of circRNAs. Covalently closed circRNAs, as the name suggests, are a class of RNAs with a circular structure. In 1976, Sanger *et al* (55) first described viroids containing 'single-stranded and covalently closed circRNAs'. Under normal circumstances, the splicing sites of normal precursor mRNAs are joined in a linear order, which generates mature linear mRNAs with a complete 5' cap and a 3' tail after modification (56). However, there is still a special splicing mechanism called backsplicing, which may join a 5' splice site to an upstream splice acceptor (3'splice site), resulting in the production of a circular RNA whose ends are covalently linked by a 3'-5' phosphodiester bond (57). Due to differences in splicing sites and different cyclization mechanisms, certain intron sequences not originally expressed to be contained in mature mRNAs may be expressed in circRNAs (58). Therefore, circRNAs may be classified into the following categories: Exonic circRNAs (59), intronic circRNAs (60) exonic-intronic circRNAs (EIciRNAs) (Fig. 2) and circRNAs generated from tRNAs (5,61). Due to the lack of a 5' cap and a 3' tail, they are strongly resistant to exonuclease and have a higher stability compared with linear RNAs (62). Since they were first discovered in viruses as early as the 1970s, circRNAs were originally thought to be rare error-splicing sequences produced during RNA splicing. However, with the recent advances in high-throughput sequencing and bioinformatics, a wide variety of circRNAs have been detected and identified (63). CircRNAs are widely expressed in humans and other mammals and have high repeatability. For instance, approximately 5-10% of circRNAs in the human brain may also be expressed in the pig brain, which reflects the high conservation of circRNAs (64). Due

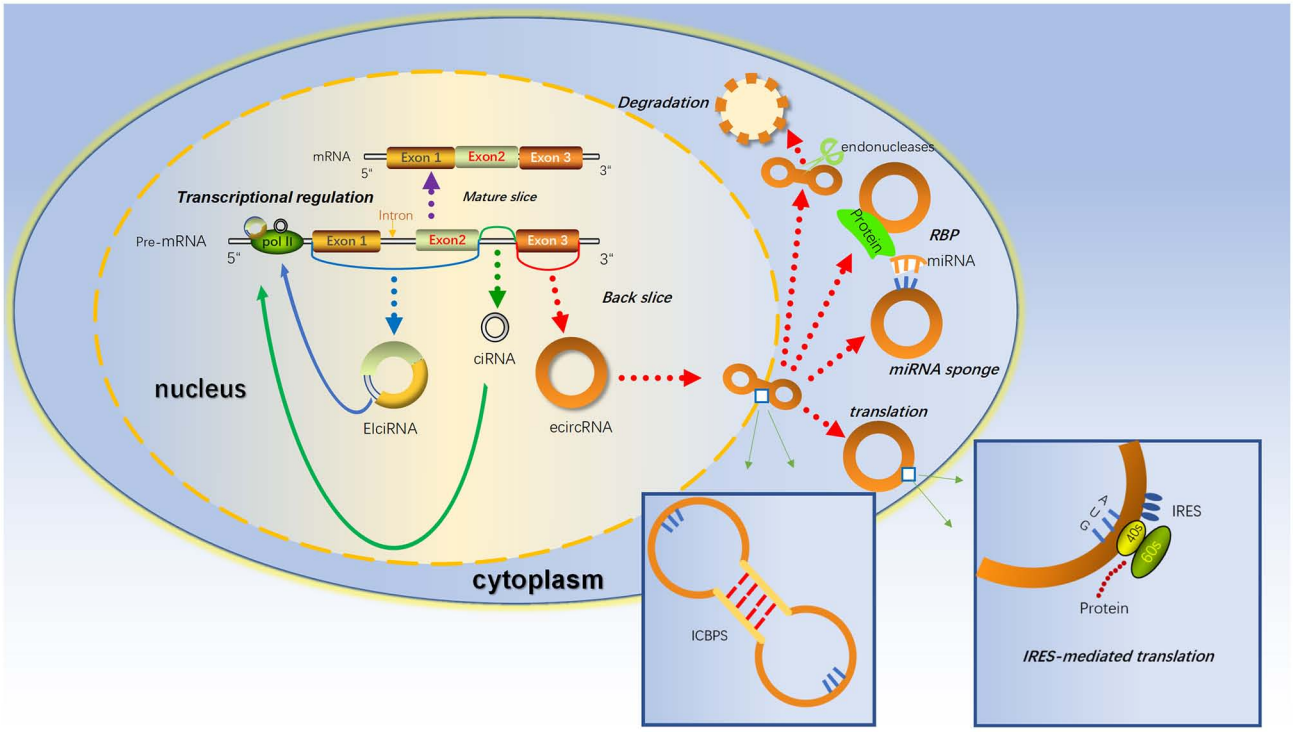

Figure 2. Generation and function of circRNAs. i) CircRNAs are generated by back-splicing of pre-mRNA, which may be divided into ecircRNAs, EIciRNAs and ciRNAs according to different splicing sites; ii) circRNAs may induce nuclear output and degradation through combining ICBPS to form a non-circular double-stranded structure; iii) the circRNAs expressed in the nucleus are mainly involved in regulating transcription, while the circRNAs expressed in the cytoplasm mainly mediate miRNA activities by sponging them; miRNA and certain circRNAs may be translated into proteins. Pol II, polymerase II; miRNA, microRNA; ElciRNA, exonic-intronic circRNAs; ciRNA, intronic circRNA; ecircRNA, exonic circRNA; ICBPS, internal complementary base pair sequences; IRES, internal ribosome entry site.

to the high abundance, relative stability and high conservation of circRNAs, the possible functions of circRNAs are gaining interest in the scientific community. According to the difference in expression sites in cells, circRNAs may be further divided into nuclear circRNAs and cytoplasmic circRNAs. Due to the isolation of the nuclear membrane, these two circRNAs may have completely different functions (65). An increasing number of studies have indicated that circRNAs expressed in the cytoplasm mostly sponge miRNAs and exert regulatory functions through competing endogenous RNA (ceRNA) mechanisms (circRNAs may sponge miRNAs to influence the stability of target RNAs or their translation, thus regulating gene expression at the transcriptional level) (66). There are miRNA binding sites in circRNAs, which may competitively bind miRNAs and reduce the regulation of downstream target genes by miRNAs. For instance, CIRS-7, the most adequately characterized circRNA with >70 conserved binding sites for miR-7 and highly stable expression in numerous tissues, particularly in neuronal tissues, where it has the potential to negatively regulate miR-7 expression and where knockout of CIRS-7 would significantly enhance the miRNA-mediated recruitment of the pluripotency gene AGO2 (67). In addition, recent studies have indicated that cytoplasmic circRNAs may interact with proteins, which are called RNA binding proteins (RBPs) (68). Similar to sponge miRNAs, circRNAs also have regions that bind to specific proteins and circRNAs may block active regions of proteins and inactivate them functionally. CircBIRC6 is enriched in the RBP-AGO2 complex and directly combines with miR-34a and miR-145 to modulate and maintain the pluripotency of human embryonic stem cells (hESCs) and suppress hESC differentiation (69). By contrast, nuclear circRNAs may exhibit more complex functions. To date, the understanding of nuclear circRNAs, whose known functions include the regulation of mRNA transcription and posttranscription, is limited. Li *et al* (70) found that EIciRNAs are incompletely spliced and have a retained intron that allows them to interact with U1 small nuclear ribonucleoprotein and promote the transcription of their host gene. In addition, although circRNAs are called noncoding RNAs, a recent study found that certain circRNAs encode proteins, and this type of circRNA has a common feature, i.e. that it has at least one open reading frame (ORF) and may be associated with polysomes. Traditionally, eukaryotic mRNAs are always translated through canonical cap-dependent translation (71). Due to the lack of a 5' cap and 3' end, circRNAs translation may only be started in a cap-independent manner. One of the alternative mechanisms, internal ribosome entry site (IRES)-mediated translation, has recently been indicated to have a key regulatory role during mammalian development (72). For instance, circ-ZNF609 contains an ORF, which has been proven by experiments to have a relatively weak translation function (73). Another important cap-independent translation mechanism is through methylated adenosine residues in the form of N6-methyladenosines (m6A) in the 5' untranslated region (74). It has been reported that certain short RNA elements containing m6A have IRES-like activity to initiate circRNA translation. Yang *et al* (75) indicated that short RNA elements for the most abundant m6A were enriched in circRNA sequences (Fig. 2).

Recently, a noteworthy study indicated that circRNA may not be 'circular': Sun *et al* (76) found a large number of internal complementary base pair sequences (ICBPS) in numerous circRNAs, particularly in 'extremely long circRNAs' (>5,000 nt); thus, they made an assumption that circRNA may not be simply circular. They may contain a double-stranded structure. This double-stranded structure has two states, 'open' and 'closed', and the process may be reversible and regulated by the microenvironment or other internal factors, such as the length of ICBPS, the binding free energy, the distance between pairing fragments and the secondary structure of RNA, or relevant RNA modifications, such as m6A. The formation of a double-stranded structure compresses circRNAs in space, which may help to facilitate circRNAs being exported into the cytoplasm from the nucleus. Furthermore, the double-stranded structure of circRNAs may make them more susceptible to degradation by related enzymes, which may explain how cells eliminate circRNAs (Fig. 2). Finally, since circRNAs are involved in numerous aspects of gene expression regulation, the association of circRNAs with cancer is considered to have great research prospects. An increasing number of studies have indicated that circRNAs may act as tumor suppressors or promoters in various human malignancies, highlighting their potential as diagnostic biomarkers and therapeutic targets for future treatment (77).

3. Role of exo-circRNAs in tumorigenesis

CircRNAs have long been considered noncoding RNAs produced during cell transcription that may exist in the nucleus or cytoplasm, and they mainly participate in gene regulation as regulators. Their functions are mainly in the parental cells. In their breakthrough study, Li *et al* (11) first revealed the enrichment of circRNAs in exosomes using high-throughput sequencing and called them exo-circRNAs. In addition, several reports have identified the abundant and stable expression of circRNAs in extracellular vesicles. At the same time, they found that exo-circRNAs were enriched in CRC, LC, breast cancer and other cancer types, and serum exo-circRNAs may distinguish cancer patients from healthy individuals (11). This provided a new way to study the mechanism of action of circRNAs. Exo-circRNAs may have several possible mechanisms and characteristics. First, exosome enrichment of specific circRNAs may be affected by their parental transcription levels (78). Furthermore, exo-circRNAs have tissue specificity, which may be related to the imbalance of gene expression regulation in related tissues during the disease process. Dou *et al* (79) generated wild-type and mutant CRC cell lines and found differentially expressed circRNAs by RNA-sequencing, some of which exist in exosomes. Quantitative PCR analysis indicated that circRNAs from exosomes expressed in wild-type and mutant cell lines exhibit obvious differences, and circRNAs were more abundant in exosomes than in cells, suggesting that exo-circRNAs may selectively have certain organization for expression and tissue specificity. More importantly, exo-circRNAs mainly regulate the function of receptor cells by targeting relevant miRNAs in receptor cells and by regulating downstream signaling pathways through ceRNA mechanisms. For instance, exosomal circ-ZNF652 promotes the proliferation, migration and invasion of hepatocellular carcinoma (HCC) cells through the miR-29a-3p/GUCD1 axis (80). This provides an important way to study the mechanism of the occurrence and progression of cancer. In addition, Dou *et al* (79) demonstrated that the circRNA content in exosomes is more abundant than that in cells, and the expression of circRNA changes with KRAS mutation. The following chapter will focus on the role of exo-circRNAs in cancer progression.

4. Role of exo-circRNAs during tumor progression

The early detection and treatment of cancer is one of the difficult problems in the medical field. More markers and therapeutic targets are required for early cancer screening. Exosomes have been recently identified as important mediators of cancer metastasis, while circRNAs have been indicated to be important regulators of tumor progression. When important vectors are associated with important modulators, a novel approach to the mechanism of tumor progression emerges. An increasing number of studies have indicated that exo-circRNAs may have an important role in the *in situ* growth, metastasis and drug resistance of malignant tumors. It was also demonstrated that exo-circRNAs not only have an important role in tumor diagnosis and prognosis as markers, but also profoundly affect the *in-situ* growth, metastasis, angiogenesis, drug resistance and treatment of malignant tumors.

Exo-circRNAs during growth. Unlimited growth is the most important characteristic of malignant tumor cells. This involves a variety of gene disorders in which exo-circRNAs may be involved. HCC is one of the most common gastrointestinal malignancies and the main reason for its occurrence is the imbalance of hepatocyte proliferation. Its occurrence may be related to cirrhosis of the liver, viral infection, fungal infection or long-term stimulation with chemical factors (81). Under the stimulation of these adverse factors, the expression of certain exo-circRNAs may change, suggesting that exo-circRNAs may be involved in the malignant transformation process of hepatocytes. Dai *et al* (82) reported that arsenite may promote the induction of malignant transformation of human liver epithelial (L-02) cells. High expression of circ-100284 was found in the transformed L-02 cell culture medium and transformed cells transferred circ-100284 to normal L-02 cells through exosomes, accelerating the cell cycle and promoting the growth of normal L-02 cells. Additional mechanistic studies indicated that exo-circRNAs may further increase the accumulation of the cell cycle-related proteins EZH2 and cyclin-D1, accelerating the G1/S transformation of the cell cycle and thus promoting l-02 cell proliferation (82). ATP produced by glycolysis is a principal energy source for HCC. As reported by Lai *et al* (83), circFBLIM1, which is highly expressed in HCC serum exosomes, may reverse the inhibition of miR-338 targeting LRP6 on HCC glycolysis, thereby promoting HCC growth and anti-apoptotic ability. Furthermore, Zhang *et al* (84) found that circ-DB was upregulated in patients with HCC with high body fat and further mechanistic studies indicated that exo-circ-DB promoted HCC growth and reduced DNA damage by inhibiting miR-34A and activating the USP7/cyclin A2 signaling pathway. By contrast, certain exo-circRNAs are involved in the negative regulation

of HCC. Chen *et al* (85) reported that circ-0051443 was transmitted from normal cells to HCC cells through exosomes and inhibited malignant biological behavior by promoting apoptosis and blocking the cell cycle. Circ-0051443 may competitively bind with miR-331-3P, releasing the more downstream apoptosis-related protein BAK1 and accelerating cell apoptosis, thus curbing the unlimited growth of hepatocellular carcinoma. In addition, Zhang *et al* (86) also found downregulated exosomal circGDI2 in oral squamous cell carcinoma, which may target the miR-424-5P/SCAI axis to regulate the malignant growth of oral squamous cell carcinoma cells. In CRC, Feng *et al* (87) found that circIFT80 was significantly upregulated in serum exosomes of patients with CRC, CRC tissues and CRC cell lines, and relevant functional tests verified that knockdown of exosomal circIFT80 inhibited the growth and cloning ability of CRC cells and increased cell apoptosis. They also investigated the relevant mechanisms and found that the circIFT80/miR-1236-3p/HOXB7 axis regulated the progression of CRC. In addition, Luo *et al* (88) found a significant increase in circulating exosomal circMYC in patients with nasopharyngeal cancer (NPC) and demonstrated via cell experiments that circMYC overexpression promoted NPC cell proliferation and enhanced cell resistance to radiotherapy. They also demonstrated that overexpression of circ-0000199 in SCC9 cells significantly promoted cell growth and reduced cell apoptosis (89). It may be concluded that the high expression of exo-circRNAs in malignant tumors may be caused by the paracrine action of tumor cells on surrounding normal cells to make normal cells malignant, or the transmission from tumor cells with a high degree of malignancy to tumor cells with a low degree of malignancy may increase the degree of malignancy. The downregulation of exo-circRNAs in malignant tumors may have the opposite effect. However, the specific transmission mechanism remains elusive and requires further discussion.

Exo-circRNAs during metastasis. Tumor metastasis has always been considered a poor prognostic factor for malignant tumors. It is important to study the mechanism of tumor metastasis to reduce the cancer stage and improve prognosis. Numerous studies have suggested that serum exo-circRNAs are important vectors for regulating tumor metastasis. Tumor metastasis involves molecular mechanisms. Li *et al* (90) indicated that exosomal circ-PDE8A in pancreatic ductal adenocarcinoma (PDAC) has an important role in tumor progression; circ-PDE8A is increased in plasma from patients with PDAC and knockout of circ-PDE8A may significantly reduce the invasion and migration of PDAC cells. Further research confirmed that circ-PDE8A acts through a ceRNA mechanism to adjust MACC1. Invasive growth of PDAC cells was stimulated by the MACC/MET/ERK or AKT pathways (90). Li *et al* (91) reported that circ-IARS expression was upregulated in plasma exosomes of patients with metastatic pancreatic cancer. Furthermore, circ-IARS was found to enter human umbilical vein endothelial cells (HUVECs) through exosomes and promote tumor invasion and metastasis. Overexpression of circ-IARS significantly downregulated the levels of miR-122 and Zo-1, upregulated the levels of RhoA and RhoA-GTP, increased the expression and adhesion of F-actin, enhanced endothelial monolayer permeability and promoted tumor invasion and metastasis (91). EMT is a crucial cause of distant metastasis of tumor cells. Chen *et al* (92) found that circPRMT5 was upregulated in serum and urine exosomes from patients with urothelial carcinoma of the bladder (UCB) and was significantly associated with tumor metastasis. Their cohort study indicated that there may be a circPRMT5/miR-30c/SNAIL1/E-cadherin pathway, which is of great significance for promoting the metastasis of UCB (92). In CRC, hypoxic cancer cells tend to have a higher metastatic potential than oxygen-rich cancer cells. Yang *et al* (93) found that circ-133 was enriched in the plasma exosomes of patients with CRC and further studies proved that circ-133 from hypoxic cells were delivered into normoxic cells and promoted cancer metastasis by acting on the miR-133a/GEF-H1/RhoA axis. Similarly, Zhao *et al* (94) reported that exosomal circ-ABCC1 derived from CD133+ cells isolated from CRC cells induced the metastasis of CRC cells, exacerbating the malignant potential of CRC cells. In GC, Lu *et al* (95) determined that circ-RanGAP1 was significantly upregulated in plasma exosomes of patients with GC at the preoperative stage, and plasma exosomes derived from these patients enhanced the migration and invasion of GC cells. In terms of the mechanism, circ-RanGAP1 may mediate the miR-877-3P/VEGFA axis to promote GC metastasis. Hui *et al* (96) also found that circNHSL1 was highly expressed in exosomes derived from GC cells, and its knockdown hindered the migration and invasion *in vitro* and inhibited tumor growth *in vivo* via the miR-149-5p/YWHAZ axis in GC. In LC, He *et al* (97) found exo-circ-0056616 by researching circRNAs significantly associated with chemokine receptor CXCR4 and confirmed its influence on the migration and invasion ability of lung adenocarcinoma cells through cell testing. Clinical sample analysis also confirmed that exo-circ-0056616 is correlated with lymph node metastasis of lung adenocarcinoma (97). Likewise, Zhang *et al* (98) indicated that circSATB2 was highly expressed in NSCLC cells, which may be transferred by exosomes and promote the migration and invasion of NSCLC cells by regulating fascin actin-bundling protein 1 expression via miR-326. In HCC, Wang *et al* (99) found high expression of circPTGR1 in serum exosomes of patients with HCC with high metastasis potential. They then cocultured serum exosomes from patients with HCC with high metastasis potential with HCC cell lines, and silencing circPTGR1 significantly inhibited cell migration and invasion. Mechanistic studies revealed that circPTGR1 was able to target miR449a (99). Of note, Huang *et al* (100) also found that circ-100338 was highly expressed in serum exosomes of patients with HCC and Transwell invasion assays suggested that overexpression or knockdown of exo-circ-100338 significantly enhanced or reduced the invasion capacity of HCC cells. Furthermore, circ-100338 may also affect the vascular permeability of HUVECs and promote tumor metastasis (100). Peritoneal metastasis of ovarian cancer is considered to be an important reason for the loss of surgical opportunity in advanced ovarian cancer. Guan *et al* (101) found that circPUM1 may promote peritoneal metastasis of ovarian cancer in the form of cancer-derived exosomes. Furthermore, Zong *et al* (102) also demonstrated that the highly expressed circWHSC1 in ovarian cancer may act on peritoneal mesothelial cells in exosome forms and promote peritoneal dissemination. In conclusion, the

specific mechanism by which exo-circRNAs regulate tumor metastasis remains to be fully clarified. It may be assumed that exosomal circRNAs may promote tumor cell metastasis by mediating EMT and regulating the vascular endothelial cell gap. In addition, it may be hypothesized that exosomes carrying circRNAs may be released into the blood by remote secretion and transported to metastatic foci or target cells for long-distance transport to exert their role as exo-circRNAs in distant metastasis of tumors. The specific mechanism still requires further study.

Of note, certain powerful exo-circRNAs may modulate certain key molecules to perform multiple functions. For instance, vascular endothelial growth factor (VEGF) may promote vascular permeability, proliferation and angiogenesis. Xie *et al* (103) found high expression of circSHKBP1 in serum exosomes of GC; however, the level of circSHKBP1 in exosomes was significantly reduced after gastrectomy. CircSHKBP1 was able to sponge miR-582-3p to increase HUR expression, enhancing VEGF mRNA stability, in this way promoting the proliferation, migration, invasion and angiogenesis of GC cells. Furthermore, circSHKBP1 was able to directly bind to heat shock protein (HSP)90 to inhibit the ubiquitin-dependent degradation of HSP90, resulting in accelerated GC malignant behavior (103). In addition, Shang *et al* (104) identified a novel CRC-derived exosomal circRNA, circPACRGL. It was able to facilitate the expression of transforming growth factor-β1 (TGF-β1) through miR-142-3p/miR-506-3p. TGF-β belongs to a group of TGF-β superfamilies that mainly regulate cell growth and differentiation, and in the above study, TGF-β1 was indicated to promote the proliferation, migration and invasion of CRC cells. Furthermore, Fang *et al* (105) noticed the significance of circRNA Rho GTPase activating protein 10 (circARHGAP10) and demonstrated its high expression in serum-derived exosomes of patients with NSCLC. Inhibition of circARHGAP10-mediated glycolysis repressed proliferation, migration and invasion of NSCLC cells *in vitro*, as well as curbed tumor growth *in vivo* through the miR-638/FAM83F axis (Table I). Beyond these examples, a large number of powerful exosomal circRNAs remain to be discovered.

Exo-circRNAs during drug resistance. Drug therapy is important for the comprehensive treatment of malignant tumors and drug resistance is a major challenge in the treatment of advanced cancer. It has been indicated that the expression of certain exo-circRNAs in the serum of patients with drug resistance is severely disordered, indicating that exo-circRNAs may be involved in the progression of drug resistance in tumor cells. Platinum drugs are considered the most classic chemotherapy drugs to kill tumor cells, and their phase I clinical efficacy has been universally recognized. For instance, cisplatin is mainly used to treat testicular cancer, ovarian cancer and bladder cancer in clinical practice (106). However, with the progression of advanced tumors, the sensitivity of numerous tumor cells to platinum drugs is decreasing progressively and the mechanism is still under study. Wang *et al* (107) first found that the expression of pyruvate kinase isoenzyme 2 (PKM2) in oxaliplatin-resistant CRC cells was significantly higher than that in oxaliplatin-sensitive cells. PKM2 is a key enzyme in the glycolytic pathway and has important significance for the rapid growth and chemical resistance of tumor cells. In addition, they found high expression of ciRS-122 in serum exosomes of patients with CRC resistant to oxaliplatin and discovered the ciRS-122/miR-122/PKM2 pathway. Through *in vitro* and *in vivo* experiments, it was indicated that oxaliplatin-resistant cell exosomes delivered ciRS-122 to sensitive cells, thus promoting glycolysis and drug resistance through sponging miR-122 and upregulating PKM2 (107). Hon *et al* (108) found high expression of circ-0000338 in exosomes of HCT116 cells in CRC and knockout of circ-0000338 improved the FOLFOX resistance of CRC cells. In addition, Luo and Gui (109) observed a significant increase of circFOXP1 in circulating exosomes in patients with cisplatin (DDP)-resistant ovarian cancer and mechanistic studies indicated that circFOXP1 regulated the expression of CCAAT enhancer binding protein γ and formin-like 3 by sponging miR-22 and miR-155-3P and that miR-22 and miR-150-3p mimics may attenuate circFOXP1-mediated DDP resistance. Zhao *et al* (110) also found that circRNA-CDR1AS was downregulated in serum exosomes of patients with DDP-resistant ovarian cancer. Subsequently, inhibition of CDR1AS facilitated the expression of miR-1270, and miR-1270 exerted its role via modulating the suppressor of cancer cell invasion (SCAI) expression. In brief, CDR1AS sensitizes ovarian cancer to DDP by regulating the miR-1270/SCAI signaling pathway. Similarly, Yao *et al* (111) also found DDP resistance in GC. In the serum and cells of patients with DDP-resistant GC, exo-circ-PVT1 was upregulated, while miR-30a-5p was downregulated. Mechanistic studies indicated that there was an exosomal circ-PVT1/miR-30a-5P/YAP1 axis that regulated autophagy, invasion and apoptosis in GC cells to promote DDP resistance. Beyond the role of exo-circRNAs in platinum-based chemotherapy-drug resistance, Han *et al* (112) found circ-HIPK3 to be obviously increased in temozolomide (TMZ)-resistant glioma cells and their exosomes. Exosomal circ-HIPK3 was able to aggravate TMZ resistance by regulating the miR-421/ZIC5 axis in TMZ-resistant glioma. Similarly, Ding *et al* (113) found that exosomal circNFIX enhanced the resistance to TMZ in glioma at least in part by sponging miR-132. In addition to chemotherapy drug resistance, exo-circRNAs also have a role in immune drug resistance, endocrine drug resistance and targeted drug resistance. Luo and Gui (114) found that circMYC expression in circulating exosomes was significantly higher in bortezomib-resistant patients with multiple myeloma than in nondrug-resistant patients. Ma *et al* (115) revealed a novel serum exosomes-based circ-0002130, which was able to target miR-498 to regulate key molecules of the glycolytic pathway, including glucose transporter 1, hexokinase-2 and lactate dehydrogenase A, thereby facilitating osimertinib resistance, which is closely related to glycolysis in NSCLC. Hu *et al* (116) found that exosomal circ-UBE2D2 is able to bind miR-200A-3P to enhance tamoxifen resistance in breast cancer. Zhang *et al* (117) found that exo-derived circUHRF1 secreted by HCC cells inhibited natural killer-cell function by upregulating the expression of TIM-3 by sponging miR-449C-5p, driving the resistance to anti-PD1 immunotherapy (Table II). In general, exo-circRNAs have great research prospects in the drug resistance of malignant tumors. In recent years, an increasing number of exosomal circRNAs

Table I. Mechanism of exosomal circRNAs regulating cancer growth and metastasis.

A, Growth

Cancer type	CircRNA	Direction of differential expression	Possible target/mechanism	(Refs.)
HCC	Circ-DB	Up	miR-34a/USP7/cyclin A2	(84)
	Circ-0051443	Down	miR-331-3p/BAK1	(85)
	CircFBLIM1	Up	miR-338/LRP6	(83)
	Circ-100284	Up	miR-217/EZH2	(82)
CRC	CircIFT80	Up	miR-1236-3p/HOXB7	(87)
OSCC	CircGDI2	Down	miR-424-5p/SCAI	(86)
	Circ-0000199	Up	NS	(89)
NPC	CircMYC	Up	NS	(88)

B, Growth and metastasis

Cancer type	CircRNA	Direction of differential expression	Possible target/mechanism	(Refs.)
CRC	CircPACRGL	Up	miR-142-3p/miR-506-3p/TGF-β1	(104)
GC	CircSHKBP1	Up	miR-582-3p/HUR/VEGF	(103)
NSCLC	CircARHGAP10	Up	miR-638/FAM83F	(105)

C, Metastasis

Cancer type	CircRNA	Direction of differential expression	Possible target/mechanism	(Refs.)
PDAC	Circ-PDE8A	Up	miR-338/MACC1/MET	(90)
	Circ-IARS	Up	NS	(91)
UCB	CircPRMT5	Up	miR-30c/SNAIL1/EMT	(92)
CRC	Circ-133	Up	miR-133a/GEF-H1/RhoA	(93)
	Circ-ABCC1	Up	β-catenin	(94)
	Circ-RanGAP1	Up	miR-877-3p/VEGFA	(95)
	CircNHSL1	Up	miR-149-5p/YWHAZ	(96)
Lung cancer	Circ-0056616	Up	NS	(97)
	CircSATB2	Up	miR-326/FSCN1	(98)
HCC	CircPTGR1	Up	miR-449a-MET	(99)
	Circ-100338	Up	NS	(100)
OC	CircPUM1	Up	NS	(101)
	CircWHSC1	Up	NS	(102)

miR, microRNA; Circ, circular RNA; NS, not specified; CRC, colorectal cancer; GC, gastric cancer; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; UCB, urothelial carcinoma of the bladder; HCC, hepatocellular carcinoma; OC, oral cancer; USP7, ubiquitin-specific protease 7; BAK1, ; LRP6, LDL receptor related protein 6; EZH2, enhancer of zeste homolog 2; HOXB7, homeobox B7; SCAI, suppressor of cancer cell invasion; TGF-β1, transforming growth factor-β1; HUR, human antigen R; VEGF, vascular endothelial growth factor; FAM83F, family with sequence similarity 83F; MACC1, metastasis-associated in colon cancer 1; EMT, epithelial-mesenchymal transition; GEF-H1, guanine nucleotide exchange factor-H1; YWHAZ, tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein zeta; FSCN1, fascin actin-bundling protein 1.

have been found to be dysregulated in drug-resistant tumor cells, which may be involved in the development of drug resistance in tumors. Currently, the known mechanism is mainly that exosomal circRNAs act as sponges of miRNAs and regulate related genes and signaling pathways involved with downstream drug targets through ceRNA mechanisms. Other relevant mechanisms remain to be elucidated.

Exo-circRNAs in cancer diagnosis and prognosis. The low efficiency of cancer diagnosis and prognosis is a problem faced by all clinicians in diagnosis and treatment. Researchers urgently need to discover a more stable and accurate indicator to diagnose cancer and judge prognosis compared to traditional diagnosis and treatment indicators. Studies have indicated that there are significantly differentially expressed

Table II. Mechanisms of exosomal circRNAs regulating cancer drug resistance.

Drug	Cancer type	CircRNA	Direction of differential expression	Possible target/mechanism	(Refs.)
Oxaliplatin	CRC	CiRS-122	Up	miR-122/PKM2	(107)
FOLFOX	CRC	Circ-0000338	Up	NS	(108)
Cisplatin	EOC	CircFOXP1	Up	miR-22/miR-155-3P	(109)
	OC	CDR1AS	Down	miR-1270/SCAI	(110)
	GC	Circ-PVT1	Up	miR-30a-5p/YAP1	(111)
TMZ	Glioma	Circ-HIPK3	Up	miR-421/ZIC5	(112)
		CircNFIX	Up	miR-132	(112)
Bortezomib	MM	CircMYC	Up	NS	(114)
Osimertinib	NSCLC	Circ-0002130	Up	miR-498/GLUT1/HK2	(115)
Tamoxifen	BC	Circ-UBE2D2	Up	miR-200a-3p	(116)
Anti-PD1	HCC	CircUHRF1	Up	miR-449c-5p/TIM-3	(117)

miR, microRNA; Circ, circular RNA; NS, not specified; CRC, colorectal cancer; EOC, epithelial ovarian carcinoma; OC, oral cancer; MM, multiple myeloma; NSCLC, non-small cell lung cancer; BC, breast cancer; HCC, hepatocellular carcinoma; PKM2, pyruvate kinase M2; SCAI, suppressor of cancer cell invasion; YAP1, yes1 associated transcriptional regulator; ZIC5, Zic family member 5; GLUT, relative protein expression of glucose transporter 1; HK2, hexokinase 2; TIM-3, T-cell immunoglobulin and mucin domain 3.

circRNA lineages in peripheral blood exosomes from certain tumor patients, suggesting that specific circRNAs may be detected after peripheral blood exosome extraction, which may be used as follow-up molecular markers to diagnose or treat this disease (118). Tumor cells may spread circRNAs by excreting them into exosomes. They may transmit biological information to specific cells to establish efficient phenotypic transmission to induce cancer. For instance, Yang *et al* (119) isolated serum exosomes from patients with NSCLC and found that exo-circRNA_102481 was able to enhance ROR1 expression, thereby promoting EGFR-TKI resistance in NSCLC. Exo-circRNA_102481 may be used as a therapeutic target and biomarker for the diagnosis of EGFR-TKI resistance in NSCLC (119). RNA-sequencing analysis indicated that exo-circRNAs in exosomes were at least 2-fold enriched compared to parental cells, for example, in patients with CRC, colon cancer patients were able to be distinguished from healthy controls by exo-circRNAs, which not only lays the foundation for the development of exosomal cancer biomarkers, but also suggests the potential biological functions of exo-circRNAs (11). Furthermore, exosomes may cross the blood-brain barrier and are readily available in almost all types of human biological fluids. Li *et al* (120) demonstrated the presence of abundant circRNAs in both high-grade astrocytoma (HGA) cells and HGA cell-derived exosomes. This also means that exo-circRNA is a promising biomarker for HGA.

Despite great advances in surgery, therapeutic radiotherapy, selection and chemotherapy in recent years, the prognosis of cancer patients remains unsatisfactory. In the study of Liu *et al* (121) in esophageal squamous cell carcinoma (ESCC), the expression of serum exosomal hsa_circ_0026611 was significantly upregulated in ESCC with lymph node metastasis, and it was a predictor of ESCC prognosis. In studies on CRC, the upregulated exosomal circular RNA-circCOG2 was indicated to promote CRC proliferation, migration and invasion through the miR-1305/TGF-β2/SMAD3 pathway. circCOG2 is associated with poor prognosis and may be used as a therapeutic target for CRC (122).

Other mechanisms. Cancer-related cachexia, which may be associated with the excessive use of fat and skeletal muscle, is one of the causes of death in patients with advanced tumors. Regarding the role of circRNAs in cancer cachexia, there is only one study in GC, which reports that ciRS-133 (circRNA hsa_circ_0010522) not only promotes the browning of white adipose tissue (WAT), but also aggravates cachexia in mice with tumor implantation. Zhang *et al* (123) found that exocrines from GC cells were able to deliver CIRS-133 to preadipocytes, promoting the browning of WAT by activating PRDM16 and inhibiting miR-133. Of note, Luo *et al* (124) found that patients with HCC with higher levels of circulating exo-circAKT3 had higher rates of tumor recurrence. There are numerous exo-circRNAs that simultaneously affect multiple biological functions of malignant tumor cells by mechanisms that remain to be elucidated.

5. Discussion

Exosomes are special extracellular vesicles with small inner diameters. They may act as carriers of proteins, RNA, DNA, lipids and other substances, participate in intercellular communication and carry the genetic information of donor cells to recipient cells to regulate the biological functions of recipient cells. CircRNAs are a type of noncoding RNA with a high abundance, conservation and relative stability. With increasing research on circRNAs, they are no longer regarded as the wrong splicing sequence produced in the transcription process. Instead, circRNAs may act as sponges of miRNAs, bind proteins and act as regulators. In addition, certain circRNAs may specifically bind to transcriptional initiation sequences and regulate RNA transcription. There are even

circRNAs with ORFs that may encode proteins under certain circumstances. Research in general on the mechanisms of circRNAs has been mainly performed in parental cells, but this cannot fully explain the role of circRNAs in distant metastasis of tumors. Of note, differentially expressed circRNAs were found in the serum of tumor patients compared to normal subjects. Further studies revealed that exo-circRNAs, as a new 'combination', may be involved in tumor metastasis, *in situ* growth, drug resistance and even tumor recurrence.

Exo-circRNAs are a new form of circRNAs. CircRNAs may be expressed not only in donor cells but also in receptor cells by acting as 'outcomers'. In summary, exo-circRNAs released into the extracellular microenvironment may be ingested by surrounding cells through paracrine signaling, regulating the *in situ* growth of malignant tumor cells, exacerbating the malignancy of tumor cells and even promoting the malignant transformation of adjacent normal cells. As demonstrated by Wu *et al* (125), exosomes from cholangiocarcinoma cells enhanced circ-0000284 expression and were able to be transferred directly from cholangiocarcinoma cells to surrounding normal cells via exosomes, and in this way stimulate the malignant biological behavior of surrounding normal cells, including proliferation and metastasis particularly. Furthermore, exo-circRNAs may enter the humoral circulation and be absorbed by distant specific target cells via remote secretion, thus indirectly affecting the metastatic ability of tumors. In addition, drug resistance has always been a manifestation of malignant tumor cells and circRNA disorders may be involved. Indications for the involvement of circulating exo-circRNAs in extensive drug resistance have been identified. When drugs enter the humoral circulation, they select the corresponding target cells to exert a role, while exo-circRNAs may selectively bind to the receptor cells targeted by drugs and enhance or weaken drug sensitivity by regulating the downstream signaling pathways. In other aspects, exo-circRNAs are also involved in tumor recurrence and immune escape, and the mechanisms remain to be further studied.

Of note, exo-circRNAs also have important clinical value in the early screening of tumor patients. Pan *et al* (126) upregulated exosomal hsa-circ-0004771 in patients with CRC and the upregulation amplitude increased significantly with the progression of the CRC stage, which has been regarded as a new potential diagnostic biomarker for CRC. Shao *et al* (127) also demonstrated that exosomal hsa_circ_0065149 was downregulated in patients with GC and the degree of its downregulation was significantly associated with the stage, survival time and lymph node metastasis of patients, which may be used as an important screening indicator for early GC. In recent studies, it was indicated that exo-circRNAs have important value in a new technique called liquid biopsy. This is an important discovery that is expected to be a new diagnostic criterion for malignant tumors. Fluid biopsies are easy to obtain blood samples taken at any point in time to monitor the disease status of patients who have a tumor by analyzing tumor cells or tumor cell products in the blood sample (128). Previously, pathological diagnosis of biopsy samples has always been considered the 'gold standard' for the diagnosis of malignant tumors, but it has certain disadvantages. First, biopsy is an invasive procedure and compared with noninvasive or minimally invasive procedures, patient compliance is insufficient. Furthermore, for patients with tumors in deep locations or small tumor lesions, biopsy is likely to give false-negative diagnoses, resulting in missed diagnoses. In addition, biopsies are usually taken from the primary tumor and reflect its current characterization at the time of sampling. However, due to the heterogeneity of the tumor, it is possible to fail to detect certain features, even the most aggressive subclones. By contrast, liquid biopsy is a minimally invasive examination that may dynamically reflect the degree of malignancy of the tumor, particularly for certain patients with small primary tumors in the early stage, and its diagnostic value will be magnified (129). However, the most critical step in liquid biopsy technology, and the most important challenge, is the selection of diagnostic markers. The current introduction of exo-circRNAs indicates that, due to their performance in early screening, they have potential as diagnostic markers in cancer.

Despite these encouraging developments, numerous deficiencies remain in the current research on the mechanisms of exo-circRNAs, and there are still numerous difficulties and challenges in the process of their formal incorporation into clinical applications. In terms of the mechanism, exo-circRNAs mainly exert their role through the ceRNA mechanism, which may be because exosomes are mainly phagocytic cytoplasmic circRNAs, thus acting according to the ceRNA mechanism of circRNAs in the cytoplasm. In addition, it is traditionally thought that, as circRNAs involved in transcriptional and post-transcriptional regulation are mainly present in the nucleus, it is difficult for nuclear circRNAs to reach the cytoplasm due to the isolation of the nuclear membrane; thus, exo-circRNAs may hardly have the role of regulating transcription and translation. The latest report of circRNAs that may not be 'circular' also proposed a new hypothesis for the study of exo-circRNAs, i.e., nuclear circRNAs may also be transported to target cells by exosomes and regulate the biological behavior of target cells at the gene level, which may better explain the powerful function of exo-circRNAs. More research is required to confirm this. Finally, exosomes carrying circRNAs secrete circulating fluid, the circRNAs are released in the target cell and then function in combination with miRNAs or proteins; thus, it may be suspected that if a new form exists in donor cells, the circRNAs will combine with both miRNAs and proteins in the form of a composition commonly taken in by exosomes. After the same mode of transportation, circRNAs are released in the target cell and then, through specific circRNA degradation, dissociative circRNAs and a combination of miRNAs and proteins, the function of specific miRNAs and proteins in parental cells may be modified. All these findings provide different ideas for future research on exo-circRNAs.

6. Conclusion

In recent years, exo-circRNAs have been a hot field in cancer research. The present review began with the origin and function of exosomes and then introduced the origin and function of circRNAs. Subsequently, the concept of exo-circRNAs and the differentially expressed exo-circRNAs most known cancers were introduced. The functions of exo-circRNAs in tumors were classified, including tumor cell growth, metastasis and malignant tumor drug resistance. The mechanisms by which exo-circRNAs regulate tumor functions were

summarized. Finally, the deficiencies and limitations of current exo-circRNA research were proposed and guidance for the future direction of exo-circRNAs was provided. It may be expected that exo-circRNAs become a hot topic for future research and emerge as potential new diagnostic markers and therapeutic targets for cancer.

Acknowledgements

Not applicable.

Funding

The present study was supported in part by the National Natural Science Foundation of China (grant nos. 82073133 and 82203486), Scientific research project of Jiangsu Health Committee (grant no. ZDA2020005), 'Six Talents Peak' High-level Talent Project of Jiangsu Province (grant no. WSW-050) and Xuzhou Medical Leading Talents Training Project (grant no. XWRCHT20210034)

Availability of data and materials

Not applicable.

Authors' contributions

JS and TJ provided direction and guidance throughout the preparation of this manuscript. JC, JW and LL collected and analyzed studies and were major contributors in writing and editing the manuscript. CZ, YZ, ZX and XS reviewed and revised the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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