Underlying metastasis mechanism and clinical application of exosomal circular RNA in tumors (Review)

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Abstract. Circular RNA (circRNA) is a long non-coding RNA molecule with a closed loop structure lacking a 5'cap and 3'tail. circRNA is stable, difficult to cleave and resistant to RNA exonuclease or RNase R degradation. circRNA molecules have several clinical applications, especially in tumors. For instance, circRNA may be used for non-invasive diagnosis, therapy and prognosis. Exosomes play a crucial role in the development of tumors. Exosomal circRNA in particular has led to increased research interest into tumorigenesis and tumor progression. Additionally, exosomal circRNA plays a role in cell-cell communication. Exosomal circRNA facilitates tumor metastasis by altering the tumor microenvironment and the pre-metastatic niche. Additionally, studies have revealed the mechanism by which exosomal circRNA affects malignant progression through signal transduction. Moreover, exosomal circRNA promotes tumor metastasis by regulating gene expression, RNA transcription and protein translation. In this review, the biological features and clinical application of exosomal circRNA are described, highlighting the underlying mechanisms through which they regulate tumor metastasis. The application of circRNA as clinical diagnostic biomarkers and in the development of novel therapeutic strategies is also discussed.

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Abbreviations: CC, colon cancer; circRNA, circular RNA; CRC, colorectal cancer; EMT, epithelial-to-mesenchymal transition; ESCC, esophageal squamous-cell carcinoma; EV, extracellular vesicle; HCC, hepatocellular carcinoma; miRNA, microRNA; MMP, matrix metalloproteinase; MSC, mesenchymal stem cell; NPC, nasopharyngeal carcinoma; RNA-seq, RNA sequencing; TME, tumor microenvironment; UCB, urothelial carcinoma of the bladder

Key words: circRNA, exosomal circRNA, TME, diagnosis, biomarker, tumor metastasis, drug resistance

Contents

1. Introduction

Circular RNA (circRNA) is a type of endogenous non-coding RNA with diverse biological functions in tumors (1). circRNA molecules are involved in the initiation of tumorigenesis and tumor metastasis. Differential expression of circRNA occurs in diverse stages of tumor progression (2). circRNA can sponge microRNA (miRNA/miR) molecules and affect mRNA translation into proteins (3).

Exosomes contain various cargos, including proteins, lipids, DNA and RNA. Exosomes mediate intercellular communication by transferring cargo between cells, including cancer cells. The exosomal contents are transferred to the recipient cell, inducing changes in gene expression and alterations to the tumor microenvironment (TME) (4,5). This process is associated with tumor metastasis. Moreover, circRNA molecules are abundant and stable in exosomes (6). Exosomal circRNA has several extracellular functions and plays critical roles following exosome uptake by recipient cells (7). Exosomal circRNA may induce trans-differentiation processes, such as epithelial-to-mesenchymal transition (EMT), macrophage polarization (8,9) and changes to the TME (10,11). These processes often impact tumor metastasis, as remodeling the extracellular microenvironment is a crucial condition for

metastasis. The distant movement of malignant cells requires changes to the pre-metastatic niche (12). However, the detailed mechanism underlying the functions of exosomal circRNA in tumor metastasis are unclear. Thus, deciphering the roles of exosomal circRNA may provide insight into the mechanism of tumor progression.

In this review, research advances into the underlying mechanism and clinical application of exosomal circRNA in tumorigenesis and metastasis are discussed. In particular, the present review focuses on the relationship between circRNA, exosomes and the TME. Furthermore, we propose that exosomal circRNA might indirectly regulate the TME, EMT and macrophage polarization, which in turn affects tumor progression. In addition, exosomal circRNA may represent a diagnostic molecular biomarker and clinical target for cancer treatment.

2. Biogenesis and function of circRNA

Sanger *et al* (13) first identified the structural characteristics of circRNA, which comprise a single-stranded, highly stable and closed loop structure lacking a 5'cap or 3'poly-A tail. Numerous circRNA molecules have been identified in eukaryotic cells and tissues and were found to be constructed from selective exonic and intronic repeats that base-pair to one another (14). The involvement of back-splicing and exon-skipping in circRNA formation have been confirmed *in vitro* and *in vivo* (15). circRNA back-splicing involves joining a splice donor to an upstream splice acceptor site. Theoretically, exons in the genome can be circularized. There are four types of circRNA molecules, which are categorized according to their method of formation: i) Exon-intron circRNA (Fig. 1A) (16); ii) exonic circRNA (Fig. 1B) (17); iii) circular intronic RNA (Fig. 1C) (18); and iv) transfer RNA (tRNA) intronic circRNA, which is formed by splicing pre-tRNA introns (Fig. 1D) (16,19). However, the most common type of circRNA is exonic circRNA. Recently, with the development of RNA sequencing (RNA-seq) technologies and novel bioinformatics approaches, numerous circRNA molecules have been detected and identified. circRNA is stable, abundant, prevalent and conserved (20). The biological functions of circRNA include acting as miRNA sponges that regulate gene expression, acting as miRNA 'reservoirs' that stabilize miRNA function, modulating gene expression via ribosome-binding proteins and even encoding proteins (21). Some protein-coding genes may actually produce both non-coding circRNA and protein (22). Das *et al* (23) have observed that circRNA generated from multiple exons can contain different combinations of these exons, due to alternative splicing, although the back-splicing junction sequence is the same. It was predicted that splice variants would be associated with different subsets of target RNA-binding proteins and miRNA and the results of this previous study showed that different circRNA splice variants can have different biological effects (23).

circRNA has several biological characteristics. It is predominantly expressed in the cytoplasm and regulates the expression of target genes by mediating miRNA activity (24). Most circRNA molecules are found at high levels in extracellular body fluids (liquid biopsy), including serum, urine, saliva and cerebrospinal fluid (25). They are highly resistant to RNA exonuclease or RNase R (26). circRNA may encode a protein under a certain conditions; for example, *in vitro* and *in vivo* evidence suggests that hsa_circ_0000423 carries an open reading frame that encodes a functional protein in colon cancer (CC) cells (27).

miRNA are small, non-coding RNA molecules that play pivotal roles in the regulation of target gene expression by regulating mRNA degradation or inhibiting translation (28). Previous studies have demonstrated that miRNA molecules are significantly associated with tumor growth, metastasis and progression (29,30). circRNA may also regulate cell signal transduction and RNA transcription via circRNA-miRNA regulatory networks that control target genes (31). Thus, circRNA can represent a switch that controls miRNA. Currently, circRNA is considered an important factor in the regulation of tumorigenesis and metastasis. For instance, hsa_circRNA_102958 expression is significantly increased in colorectal cancer (CRC) tissue and silencing the expression of this circRNA markedly suppresses CRC growth, migration and invasion (32). Moreover, hsa_circRNA_102958 acts as a sponge for miR-585, whereby hsa_circRNA_102958 promotes cell division cycle 25B expression by inhibiting miR-585 activity in CRC cells (32). The circRNA cerebellar degeneration-related protein 1-antisense (CDR1-AS) binds to miR-7 and acts as its molecular sponge (33). miR-7-5p is the mature form of miR-7 and is closely related to the occurrence and development of tumors (34). For example, miR-7 inhibits the ability of gastric cancer cells to divide, migrate and invade, while promoting their apoptosis (35). circRNA circR-7 acts as a miR-7 sponge that inhibits its biological function (36). Thus, circRNA binding to miRNA inhibits its functions and since these functions can be associated with oncogenesis, circRNA could regulate tumor cell differentiation, growth and metastasis indirectly.

The identification of circRNA functions provided a novel molecular mechanism for cancer. circRNA exerts several verified functions. For example, a previous study has demonstrated that circ-zinc finger protein 609 (circ-ZNF609), an oncogenic circRNA, is significantly upregulated in the human glioma cell lines U87 and U251 (37). In addition, circ-ZNF292 silencing suppresses tube formation by inhibiting glioma cell proliferation and cell cycle progression (38). Based on these findings, it has been proposed that abnormal miRNA or circRNA expression may alter cancer growth. Similarly, recent studies have suggested that circRNA can display tissue-dependent expression in neurodegenerative diseases (39). circRNA is differentially expressed in various tumor tissue types, including breast cancer (40), hepatocellular carcinoma (HCC) (41,42) and CRC (32).

3. Biogenesis and functions of exosomal circRNA

Exosomes are nanoscale (30-150 nm) extracellular vesicles (EVs) of endocytic origin that are shed by most types of cells and circulate in bodily fluids, such as blood, urine, saliva and breast milk (43) They contain a specific cargo of diverse growth factors, proteins, lipids and nucleic acids, including long non-coding RNA and circRNA, which can modulate recipient cell behavior and might be used as biomarkers for diagnosis, such as bladder and breast cancer (44,45). Different

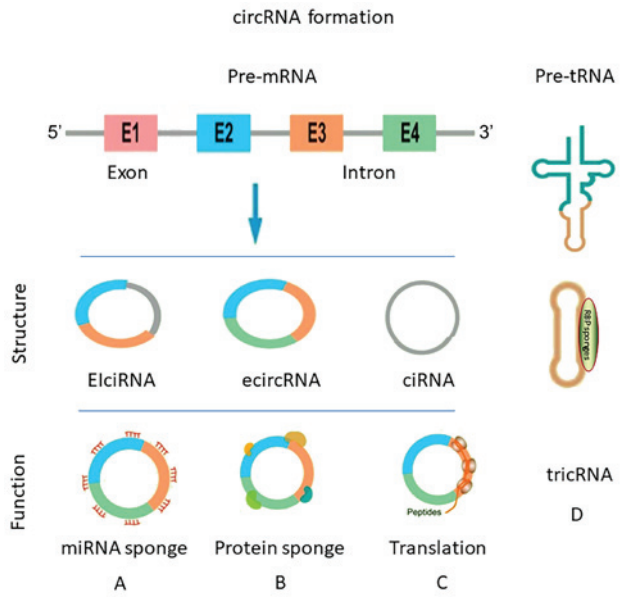

Figure 1. Structure, biogenesis and function of circRNA. (A) EIcircRNA. Exons circularized with the intervening intron sequence retained are referred to as EIcircRNA. (B) ecircRNA. ecircRNA molecules are generated by back-splicing of the 5'splice donor site to an upstream 3'splice acceptor site. (C) ciRNA. ciRNA molecules are derived from introns. (D) tricRNA. tricRNA are generated by joining pre-tRNA intronic ends. circRNA, circular RNA; EIcircRNA, exon-intron circular RNA; ecircRNA, exonic circular RNA; ciRNA, circular intronic RNA; tricRNA, transfer RNA intronic circRNA; tRNA, transfer RNA.

of exosomes can carry these cargos from cell to cell and mediate intercellular communication. In cancer progression, exosomal cargos are the link between the disruption of normal tissues and oncogenesis (46). Exosomes can facilitate tumor progression by altering their contents and remodeling the microenvironment, thus accelerating the progression of oncogenic processes (44).

RNA-seq analysis has revealed that circRNA are present in exosomes, representing a novel class of RNA species in exosomes, which might be regulated by the levels of associated miRNA in cells and result in the transfer of biological cargos into recipient cells (47). In addition, a previous study has suggested that the concentration of circRNA in exosomes is greater in cholangiocarcinoma cells than in normal cells (48). To date, >1,000 exosomal circRNA molecules have been identified in human serum. For example, circ-kelch domain containing 10 was identified in a patient with CRC, and it has been demonstrated that this circRNA could be measured by RNA-seq and further validated individually with quantitative reverse transcription PCR analysis in serum from cancer patients (7). Therefore, exosomal circRNA could be used to screen for tumors using patient serum, representing a new type of diagnostic biomarker for cancer (7). Another study has demonstrated that adipose-derived exosomes mediate the delivery of circRNA and promote the tumorigenesis of HCC (42).

Exosomal circRNA not only induces tumorigenesis of HCC by affecting cell signaling, but also facilitates HCC metastasis. Su *et al* (49) reported that circRNA CDR1-AS was directly transferred from HCC cells into the surrounding normal cells via exosomes, thereby mediating the proliferative and migratory abilities of surrounding cells. Moreover, it was observed that CDR1-AS could sponge miR-1270 and facilitate the expression of α-fetoprotein, a specific biomarker of HCC (49). Another study by Shen *et al* (36) has also provided insight into the association between exosomal circRNA and tumor metastasis. Therefore, exosomal circRNA may represent a future therapeutic target for tumor metastasis in clinical applications (36).

Exosomes alter the TME and facilitate tumor metastasis. Tumor metastasis is a complex process that involves genetic mutations and TME changes. Evidence shows that the TME facilitates tumor initiation and metastasis. Indeed, the TME comprises multiple categories of substances, such as T cells, exosomes, tumor-associated macrophages (TAMs), cytokines, fibroblasts, endothelial cells, mesenchymal stem cells (MSCs) and neutrophils, which exert a great influence on cancer growth and generate a pre-metastatic niche favorable to tumor progression (50-52). The pre-metastatic niche is a pre-formed microenvironment made possible by exosomes secreted by the primary tumor site before widespread metastasis (53).

Exosomes are released into the TME and bloodstream, subsequently acting as messengers that impact distant tissues (54). Exosomes release various substances into the extracellular milieu to accelerate tumor cell migration. For example, cancer stem cell exosomes might target cancer cells and organs, leading to higher capacity of clear cell renal cell carcinoma to the metastasize to the lungs (55). Matrix metalloproteinases (MMPs) can be transferred by exosomes to facilitate cancer cell invasion by degrading the extracellular stroma (56). Stromal infiltration alters the TME and facilitates tumor metastasis (57). As a constituent of exosomes, exosomal circRNA molecules are directly and indirectly involved in the crosstalk between the TME and tumor cells. The diverse intercellular exchange of exosomal circRNA might drive tumor metastasis.

EVs are circular membrane fragments released from the endosomal compartment as exosomes or shed from the surfaces of the cell membranes. They comprise a lipid bilayer membrane, forming a vesicle containing several types of biomolecules, including proteins, lipids, polysaccharides and nucleic acids. These membrane fragments can be transferred to a recipient cell. When the recipient cell absorbs the biomolecules, changes to the function and gene expression of the recipient cells are elicited (58,59).

Exosomal circRNA regulates TAM differentiation to accelerate tumor metastasis. Non-coding RNA derived from exosomes might stimulate the clearance function of macrophages. TAMs are key cells that create an immunosuppressive TME by inhibiting immune checkpoint proteins to release T cells (60). Macrophages can display very different functions depending on the nature of the microenvironment, such as cancer and inflammatory environments. Activated macrophages are classified into M1 (classically-activated macrophages) and M2 (alternatively-activated macrophages) phenotypes (61). Activated M1 macrophages exhibit anti-tumor activity and elicit anti-tumor adaptive immunity in the early stages of carcinogenesis. Activated M2 macrophages tend to display an immunosuppressive phenotype, suppress tissue repair and

promote tumor progression (62). However, M2 macrophage differentiation facilitates tumor cell immune escape; however, the exact ratio of M2/M1 macrophages in response to tumors is unclear (63).

TAMs play multi-functional roles in tumor progression, including cancer initiation and promotion, immune regulation, metastasis and angiogenesis (60). Activated M2 macrophages accumulate in the TME and facilitate tumor cell metastasis. Increased levels of exosomes may modulate the expression of proteins and stimulates M1 macrophages, which can result in the removal of cancer cells. However, further research is needed to test this hypothesis.

Exosomal circRNA molecules affect target genes in order to facilitate biological functions through communication between different cell types. This characteristic distinguishes exosomal circRNA from classical endocrine circulating RNA. In a recent study, exosomal circRNA could be transported throughout the whole body, thus acting as critical mediators of intercellular communication and inducing neoplasm metastasis (64). A previous study has suggested that the level of exosomal circRNA might reflect the expression levels of these circRNA in cells and the physiological activity of the cells to a certain degree (65). CDR1-AS, also known as CiRS-7, a circRNA sponge for miR-7, was confirmed to have ~70 conserved binding-sites for miR-7 (66). CDR1-AS expression levels are increased at metastasis sites compared with primary sites (65). Zou *et al* (67) have suggested that CDR1-AS plays a specific role in immune and stromal cell infiltration in tumor tissue. They observed that high CDR1-AS expression was associated with a higher proportion of M2 macrophages. Moreover, CDR1-AS expression correlated negatively with the number of $CD8^+$ T cells, activated natural killer cells, monocytes and neutrophils and correlated positively with the M2/M1 macrophage ratio.

CDR1-AS regulates the TGF-β signaling pathway and alters the TME (67). Stimulating TGF-β signaling can exert a great influence on the TME by remodeling the extracellular matrix (67,68). Moreover, exosomal circRNA likely accelerates M2 macrophage differentiation by altering the TME through the TGF-β signaling pathway (Fig. 2A).

Exosomal circRNA triggers EMT to promote tumor metastasis. EMT is essential in tumor metastasis. During EMT, epithelial cells lose their polarity and obtain invasive properties to become MSCs (69). Exosomal circRNA is closely associated with EMT in tumors (70). Chen *et al* (71) have demonstrated that exosomal circ-protein arginine methyltransferase 5 (circ-PRMT5) was upregulated in patients with urinary carcinoma of the bladder (UCB) and might predict metastatic progress. Indeed, upregulated exosomal circ-PRMT5 was positively associated with advanced clinical stage and poor survival. In addition, circ-PRMT5 also promoted EMT in UCB.

Other studies have also indicated that exosomal circRNA might induce EMT. In a mouse model, Zhang *et al* (72) investigated the role of exosomal circ-nuclear receptor interacting protein 1 (NRIP1) in distant metastasis via tail vein injection of gastric cancer cells co-cultured with exosomes. This study confirmed that exosomal circ-NRIP1 could promote EMT and metastasis *in vivo* (72). However, in another study, the opposite observation was made (73).

CDR1-AS1 binds to miR-7, which inhibits insulin like growth factor 1 receptor expression, thereby increasing the expression of E-cadherin to partially reverse EMT, subsequently inhibiting tumor cell metastasis (Fig. 2B) (74).

4. Bidirectional biological function of exosomal circRNA secreted by mesenchymal stem cells

Human MSCs restore damaged tissues in the body. MSCs may migrate to tumor sites and secrete a variety of factors, such as VEGF and platelet-derived growth factor (75). Exosomes exert number of functions that induce and support regenerative processes in necrotic tissue (76). MSC-derived exosomes also have antitumor effects. Exosomes derived from placental MSCs selectively inhibit the growth of prostate cancer cells through numerous molecular species within their cargo, such as mRNA, miRNA, lipids and proteins (77). MSC-derived exosomes transport mRNA and non-coding RNA to target cells and induce endothelial cell proliferation (78). For example, the transfer of miR-143 from MSC-derived exosomes to recipient cells can decrease the migration of osteosarcoma cells *in vitro* (79). Moreover, tumor cells can also reprogram surrounding MSCs to support the growth of tumors via intercellular communication, especially by releasing EVs. This long-term 'education' by tumor cells favors tumorigenesis (80). MSCs may secrete exosomes to promote the migration and invasion of breast cancer cells (81).

circRNA controls MSC identity and differentiation by sponging miRNA. For example, circ-forkhead box P1 (circ-FOXP1) is also enriched in MSCs. Silencing circ-FOXP1 expression markedly impairs MSC differentiation, Indeed, a previous study demonstrated that circ-FOXP1 regulates MSC molecular networks through the Wnt pathway (82). Tumor-derived exosomes also regulate MSCs in the distant metastatic microenvironment to promote metastasis (83). However, further experiments are required to verify the regulatory relationship between MSCs and exosomal circRNA.

Exosomal circRNA sponges miRNA and accelerates tumor metastasis. Tumor cells affect surrounding cells through direct contact, paracrine secretion and autocrine secretion (84). Intercellular communication can occur via exosomes, which has an important role in tumor metastasis and invasion (85). Exosomes containing non-coding RNA molecules are detectable in body fluids, particularly the blood, and are frequently released by tumor cells, implying that exosomes can act as messengers between cancer cells and immune cells to promote cancer cell escape from immune surveillance, thus contributing to tumor formation (86). As aforementioned, a previous study has indicated that circRNA is abundant and stable in exosomes and can continue to exert its role following uptake by recipient cells (7).

Metastasis is a phenomenon that can occur in the majority of cancer types. Tumor cells and normal cells can communicate with each other through exosomes, which secrete substances that affect tumor metastasis (87). The first metastasis mechanism occurs when exosomal circRNA induce the progression of a tumor by regulating cell signal transduction

pathways (88). In ovarian cancer cells, circ-Wolf-Hirschhorn syndrome candidate 1 binds to miR-145 and miR-1182, which upregulates the expression of downstream targets mucin 1 and telomerase reverse transcriptase, thus promoting proliferation and invasion (89). It can also facilitate peritoneal dissemination via exosomes (89). Li *et al* (90) also found that high expression levels of exosomal circ-phosphodiesterase 8A (circ-PDE8A) in pancreatic ductal adenocarcinoma tissue was positively associated with invasion. Further research revealed that circ-PED8A promoted tumor cell growth by upregulating the MET proto-oncogene (91). Exosomal circRNA also regulates the progress of tumor metastasis via cell signal transduction. Moreover, circ-protein phosphatase 1 regulatory subunit 12A (circ-PPP1R12A) encodes a conserved 73-amino-acid peptide, PPP1R12A-C, which promotes the proliferation, migration and invasion of CC cells by activating the Hippo/YES-activating protein signaling pathway (27). Another study suggested that exosomal circ-NRIP1 promoted energy production by activating the protein kinase B/AKT/mTOR signaling pathway to facilitate gastric cancer tumor growth (72). Moreover, exosomal circ-NRIP1 promoted gastric cancer metastasis via EMT (72).

The second mechanism of tumor metastasis occurs through endothelial monolayer permeability and tumor cell invasion. In pancreatic cancer cells, exosomal circ- isoleucyl-tRNA synthetase 1 (circ-IARS) increases the expression levels of RhoA and F-actin and downregulates zona occludens-1, which increases the permeability of endothelial monolayer cells (92). Animal experiments have confirmed that circ-IARS can increase the number of tumor cells that can pass through the endothelial monolayer, which promotes metastasis (92).

Other evidence has suggested that exosomal circRNA modulates tumor cell migration by sponging miRNA, thus affecting metastasis. Exosomal circRNA may shorten the duration of tumor metastasis by sponging miRNA and regulating mRNA expression. For example, circ-PTGR1 is detectable in three HCC cell lines, namely the non-metastatic HepG2, the low-metastatic 97L and the highly metastatic LM3 cell lines (91). Exosomal circ-prostaglandin reductase 1 (circ-PTGR1) derived from highly metastatic HCC cells can promote metastasis in cells that normally have low metastatic potential (93). In particular, LM3 exosome-derived circ-PTGR1 promotes the progression of HepG2 and 97L cells *in vitro* and *in vivo*, which results from circ-PTGR1 competing with MET to target miR-449a. Thus, circ-PTGR1 can promote migration and metastasis in HCC through the circ-PTGR1/miR-449a/MET pathway (93).

In tumor tissues, exosomal circRNA mediates the progression of cancer by modulating surrounding normal cells to accelerate invasion and metastasis. Su *et al* (49) found that exosomal circRNA CDR1-AS from HCC cells accelerated the proliferative and migratory abilities of surrounding normal cells. Exosomal circRNA CDR1-AS serves as a competing endogenous RNA (ceRNA) to promote the progression of HCC (94). It is directly transferred from HCC cells to surrounding normal cells via exosomes to further mediate its biological functions (49). In nasopharyngeal carcinoma (NPC) tissues, CDR1-AS upregulates E2F transcription factor 3 expression by binding to miR-7-5p, which promotes the growth of NPC cells. Moreover, CDR1-AS could promote NPC progression by negatively regulating miR-7-5p in a nasopharyngeal carcinoma xenograft tumor model (95).

In prostate cancer, exosomal circRNA acts as miRNA sponge to induce EMT and facilitate tumor cell migration and invasion. Li *et al* (96) found that exosome circ-0044516 was significantly upregulated in patients with prostate cancer and in cell lines. Exosomal circ-0044516 downregulates miR-29a-3p expression, which inhibits the progression of prostate cancer cells (96). High expression levels of exosomal circ-0000284 enhance the migration, invasion and proliferation abilities of cholangiocarcinoma cells by acting as a ceRNA that binds to miR-637, further regulating lymphocyte antigen 6 family member E expression *in vivo* and *in vitro* (97). In bladder cancer, circ-homeodomain interacting protein kinase 33 suppresses bladder cell migration, invasion and angiogenesis by sponging miR-558, which subsequently inhibits heparanase, MMP-9 and VEGF expression in vitro (98) (Fig. 2C).

5. Clinical applications of exosomal circRNA in cancer

Currently, clinical therapeutic progress includes improvements in early diagnosis, surgery, radiotherapy, chemotherapy and other types of therapeutic methods. Early effective diagnosis biomarkers are insufficient. Final diagnosis is often established by performing a biopsy, which may delay early diagnosis of the majority cancer patients. Biopsies can be painful, invasive for the patients and can lead to associated complications. Nevertheless, non-invasive early diagnostic biomarkers are lacking for clinical use and many types of carcinoma lack an authoritative indicator. Thus, exosomal circRNA could be developed as authoritative indicators. Interestingly, a previous study has shown circRNA are abundant and stable in exosomes, which can be detected in the circulation and urine (99). The most effective approach is RNA-seq analyses detection of circRNA molecules in exosomes (100,101).

Exosomal circRNA may represent diagnostic biomarkers in cancer. There is an urgent need to identify novel diagnostic biomarkers and develop more efficient therapeutic molecular targets in cancer. A recent study has revealed that the exosomes secreted by tumor cells are more abundant compared with those from normal cells (102). In addition, the contents of exosomes are different under normal physiological conditions compared with pathological conditions, even for the same tissue or body fluid (103). Exosomal circRNA is resistant to degradation and its secretion into the extracellular environment could be exploited in many biological applications; for example, as novel diagnostic biomarkers. For example, exosomal circRNA has been proposed as a potential diagnostic biomarker of idiopathic membranous nephropathy (104). A previous study has shown that both esophageal epithelial cells and esophageal squamous-cell carcinoma (ESCC) cells secrete exosomal circRNA and suggested that circRNA from patient plasma could be used for early diagnosis (105). hsa-circ-0001946 and hsa-circ-0043603 are found in exosomes of cell-conditioned culture conditioned media and may be potential diagnostic biomarkers for ESCC (106).

High-throughput sequencing analysis has demonstrated that the expression levels of three types of circRNA (hsa-circ-007293, hsa-circ-031752 and hsa-circ-020135) are

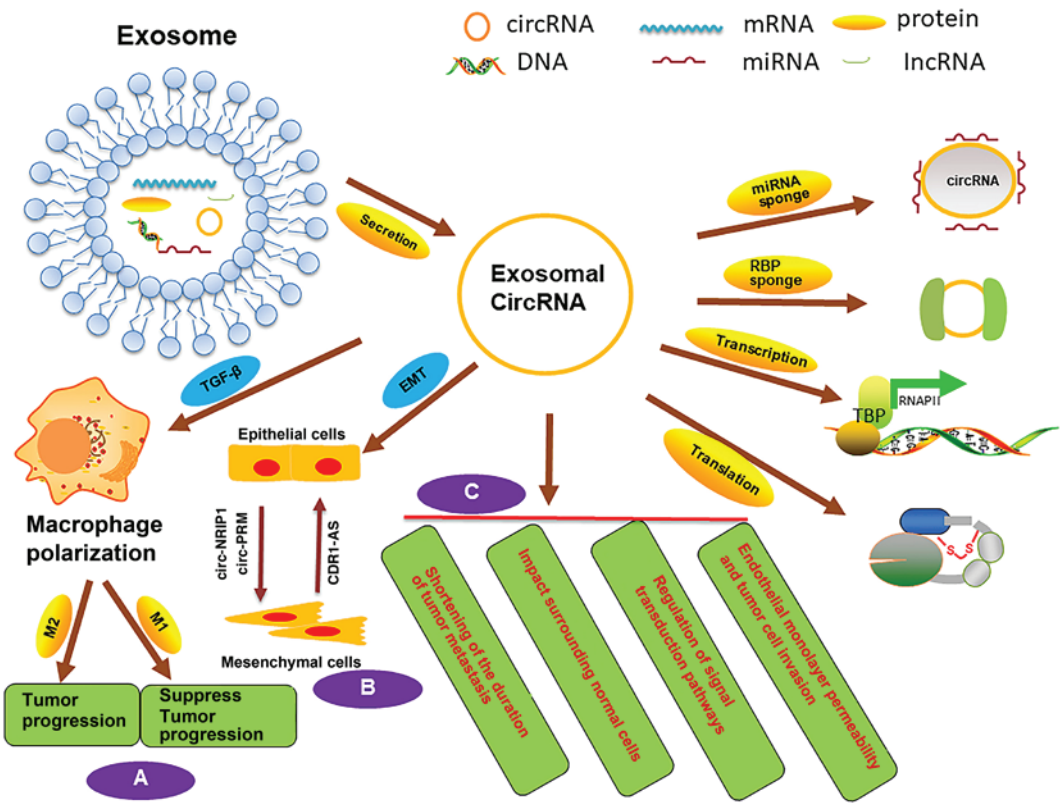

Figure 2. Schematic representation of exosomal circRNA biological functions. (A) Exosomal circRNA regulates tumor progression by indirectly impacting on TAM differentiation. (B) Exosomal circRNA molecules promote the process of EMT. (C) Underlying mechanism of tumor metastasis. CDR1-AS, CDR1-antisense; circRNA, circular RNA; circ-NRIP1, circ-nuclear receptor interacting protein 1; EMT, epithelial-to-mesenchymal transition; miRNA, microRNA; lncRNA; long non-coding RNA; RBP, ribosome-binding protein; RNAPII, RNA polymerase II; TAM, tumor-associated macrophages. TBP, TATA-binding protein; circ-PRM, circular protein arginine methyltransferase.

upregulated in the serum of patients with papillary thyroid carcinoma. Thus, these exosome circRNA might represent potential diagnostic molecular biomarkers (107).

In cholangiocarcinoma, exosome-transmitted circ-0000284 stimulates the migration and proliferation of surrounding normal cells and promotes the progression of the tumor; thus, exosomal circ-0000284 may serve as a potential metastatic diagnostic biomarker (97). Exosomal circ-PTGR1 is abundant and aberrantly expressed in malignant cells of patients with metastatic HCC. Thus, circ-PTGR1 could act as a prognostic biomarker and therapeutic target (93). Circulating exosomal hsa-circ-0004771 is significantly upregulated in patients with CRC and may serve as a novel potential diagnostic biomarker of CRC (108). A previous study also suggested that hsa_circ_0001492 and hsa_circ_0001346 might be novel potential early diagnosis candidate markers in lung adenocarcinoma (109). Altogether, these studies indicated the possibility of using circRNA as tumor diagnostic markers. However, further research remains to be done to in different diseases and tumor subtypes.

Exosomal circRNA is associated with drug resistance. Drug resistance (chemotherapy insensitivity) is common during cancer therapy. Exosomal miRNA associated with drug resistance have been revealed in certain types of cancer, such as ovarian cancer (110). However, the detailed molecular mechanism underlying the relationship between exosomal circRNA and drug resistance is unclear and should be investigated to develop new target drugs. A study has highlighted epigenetic changes, such as resistance to cytotoxic drugs and angiogenic properties conferred by exosomes in the recipient cells through this 'cargo delivery' process (111). Zhao *et al* (112) have proposed that exosomal circRNA affects drug sensitivity. CDR1-AS is 1,500 nucleotides in length and is transcribed in the antisense orientation with respect to the CDR1 gene. Upregulation of exosomal CDR1-AS could increase the cisplatin sensitivity of ovarian cancer cells (112). CDR1-AS functions as a molecular sponge for miR-1270, which weakens the inhibitory effect of the miRNA on the downstream target gene suppressor of cancer cell invasion (113). CDR1-AS might regulate the sensitivity of ovarian cancer cells to cisplatin and the progression of ovarian cancer (112,114). Modulating the release of exosomal circRNA might be a potential therapeutic strategy to improve drug sensitivity in tumors. However, further trials are required to test this hypothesis.

6. Conclusions

Exosomal circRNA has stable biological function and structure. Importantly, circRNA is resistant to degradation by RNA exonuclease or RNase R and easily obtained from body fluid or serum (115). Recently, exosomal circRNA molecules have been proposed as novel cancer diagnostic biomarkers that can be extracted non-invasively. They have been used to study cancer progression and to evaluate prognosis. Several studies have demonstrated that exosomes are closely related

to tumor development. The function of exosomes as biological delivery vehicles is of considerable interest in cancer research because modulating the TME using variety of RNA species may help increase the sensitivity of chemotherapeutics. Exosomal circRNA might promote the generation of the TME. Upregulation of exosomal circRNA expression can aggravate tumor progression. By contrast, downregulation of exosomal circRNA expression might inhibit tumor metastasis. The exosomal circRNA functions that impact on tumor progression can be divided into three pathways: i) sponging miRNA and regulating its function; ii) regulating transcription and translation; and iii) interacting with proteins to modulate gene expression. Thus, an improved understanding of exosome circRNA characteristics and functional roles in tumor progression is required. Although exosomal circRNA are known to display various functions, controlled studies in the majority of disease are lacking. In conclusion, it is essential to understand the detailed molecular mechanisms underlying the functions of exosomal circRNA, as this may lead to the development of novel diagnostic tools and treatment targets for tumors. Thus, further investigation of exosomal circRNA candidates and tumor metastasis may contribute to the control of cancer.

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Authors' contributions

XW wrote and edited the manuscript. BY was involved in acquisition of the data and provided direction and guidance throughout the preparation of this manuscript. XM generated the figures and revised the manuscript. YS, ZD and PW conceived the review and revised the manuscript. All authors read and approved the final manuscript. YS and ZD confirm the authenticity of the data.

Ethics approval and consent to participate

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests

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