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Exosomal circRNAs: biogenesis, effect and application in human diseases

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Abstract

Exosomes have emerged as critical mediators of intercellular communication, both locally and systemically, by regulating a diverse range of biological processes between cells. Circular RNA (circRNA) is a novel member of endogenous noncoding RNAs with widespread distribution and diverse cellular functions. Recently, circular RNAs have been identified for their enrichment and stability in exosomes. In this review, we outline the origin, biogenesis and function of exosomal circRNAs as well as their roles in various diseases. Although their precise roles and mechanisms of gene regulation remain largely elusive, exosomal circRNAs have potential applications as disease biomarkers and novel therapeutic targets.

Keywords: Exosome, CircRNA, Exosomal circRNA, Tumor microenvironment, Biomarker

Background

In the past 30 years, one of the most revolutionary contributions to cell biology was the discovery of exosomes; exosomes are nanoscale (30–150 nm) extracellular vesicles of endocytic origin that are shed by most types of cells and circulate in bodily fluids such as blood, urine, saliva, and breast milk [1]. Exosomal contents have been shown to be broad, composed of various growth factors, proteins, lipids, and nucleic acids, long noncoding RNAs and circular RNAs (circRNAs) [2]. Exosomes are intraluminal vesicles generated within the endolysosomal system and secreted by the fusion of multivesicular endosomes (MVEs), which are shed from the plasma membrane [3]. CircRNAs get its closed loop structures from back-spliced exons in nucleus. After transferring into cytoplasm, circRNAs can not only bind with miRNAs or protein to exert various functions, but can be sorted into MVEs along with an abundant cargo of other nucleic acids, lipid and proteins [4]. Then exosomes are secreted from the parent cells into bodily fluid, through which circRNAs start their circulation and activate their biological functions.

After released into the extracellular environment, exosomes can reach recipient cells and deliver their cargos (like circRNAs) to elicit functional responses and induce a series of phenotypic changes. Some groups reported several mediators of specific interactions contribute to exosomes to find their target cells, including integrins, lipids, lectins, and extracellular matrix (ECM). For example, exosomes-derived from cancer cells can be targeted to specific organs, such as liver and lung to promote the formation of premetastatic niche dependent on their integrin composition [5]. Additionally, membrane vesicles of cellular origin expose adhesion molecular on their surface, which could favor their capture by target cells [6].

Importantly, an increasing number of studies have focused on understanding the function of exosomes in mediating intercellular communication, tumor microenvironment, immune system functions [7–9], development and differentiation, cell signaling and viral replication [10]. Not only are exosomes reported in practical applications, they are also utilized for clinical diagnostics and therapeutic development. To summarize, exosomes are being intensively investigated as a valuable source of novel biomarkers due to the specific cargo loaded by their progenitor cells.

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Circular RNAs, a novel class of endogenous noncoding RNAs, are characterized by their covalently closed loop structures without 5′ caps and 3′ poly tails. They were first proposed in RNA (ribonucleic acid) viruses as a viroid in 1976 and were thought to be a result of splicing errors for several decades [11]. Currently, with the development of deep RNA sequencing (RNA-seq) technologies and novel bioinformatic approaches, abundant and diverse circRNAs have been detected and identified, including few circRNA functions, such as regulating transcription in the nucleus [12, 13], functioning as efficient microRNA sponges [14–16], competing with pre-mRNA splicing [17], and serving as circRNA-protein interactions [18]. Additionally, recent studies have shown that circRNAs are abundantly present in the hematopoietic compartment [19] and participate in neuronal development [20, 21]; some circRNAs are reported to be associated with the initiation, progression and metastasis of tumors [22–24]. In addition to these encouraging advances, it is worthwhile to note that their high abundance, relative stability, and evolutionary conservation among species endow circRNAs with utility as potential biomarkers for many diseases, especially for cancers [25, 26].

Interestingly, recent studies have shown that circRNAs are enriched and stable in exosomes, which can be detected in the circulation and urine [27]. For instance, it was reported that circRNAs in gastric cancer (GC) could be transferred to recipient cells via exosome delivery, suggesting that exosomal circRNAs play significant roles in the invasion and peritoneal metastasis of GC [28]. Moreover, exosomal circRNAs were also found in platelet-derived extracellular vesicles [29], hepatic cells [30] and pancreatic cancer cells [31]. Studies have reported that it is possible that cells could transfer circRNAs by excreting them in exosomes. Because exosomes can be received by many types of cells, including macrophages, they may also act as messengers in cell-to-cell communications. Interestingly, some other studies have concluded that the clearance of intracellular circRNAs was associated with exosomes, and exosomes themselves could be further removed by the reticuloendothelial system or secreted by the kidneys and liver [32, 33].

In this review, we briefly address the significance and role of exosomes as intercellular communication cargo in various diseases, including tumors, neurodegenerative disease, infections and autoimmune disorders, by transferring DNA, RNA, proteins and lipids, with a focus on circRNAs. Recent advances in exosome-derived circRNA isolation will also be discussed along with their major technical challenges. Particularly, we summarize the role of exosomal circRNAs in the formation of some diseases along with their biological functions, with an emphasis on their potential as promising diagnostic molecular markers and therapeutic targets.

Emerging roles of exosome in physiological and pathological status

Notably, it is increasingly evident that exosomes play an important role not only on the regulation of normal physiological status, such as tissue regeneration [34], immune surveillance [35], blood circulation [36] and stem cell plasticity [37], but also in the pathological conditions in several diseases. For example, exosomes take participate in tissue repair via delivering specific cargoes to the recipient cells. They can enhance the function of regulatory T cells and suppress the CD8$^+$ cell and natural killer (NK) activity. In the blood circulation, exosome also take part in breast cancer with lung metastasis from docking Nano platform [38]. Exosomes have been shown in converting the hematopoietic stem cells (HSCs) phenotype into liver cells phenotype [39].

Apart from their fundamental roles in physiological condition, exosomes have a pivotal role in disease pathogenesis, especially in tumor progression. For example, the activated PMN (polymorphonuclear leukocyte) exosomes could bind and degrade extracellular matrix (ECM) by the integrin Mac-1 and NE, respectively, inducing the disorders of chronic obstructive pulmonary disease (COPD) and bronchopulmonary dysplasis (BPD) [40]. A key study showing the clinical relevance and linkage of exosome to disease was reported in 2012 by Wan J and colleagues. This study represented that exosome core component gene was responsible for pontocerebellar hypoplasia and spinal motor neuron degeneration.

Roles of circRNAs in normal physiology and pathological status

Some circRNAs are extraordinarily enriched in the mammalian brain [26] and preferentially back-spliced in neuronal cell lines [41], suggesting that circRNAs have a potential to regulate synaptic function. Similarly, many circRNAs are significantly enriched in synaptogenesis than their linear isoforms during central nervous system aging [42]. In addition, circRNAs are associated with disease pathologic processes. For instance, circRNAs act as microRNA (miRNA) sponges to modulate gene expression. For example, circRNAs are relatively abundant in the brain [26] and accumulate to a high level during the central nervous system aging [42]. Specifically, the circRNA ciRS-7 (also termed CDR1as), which harbors more than 70 conventional miR-7-binding locations, has been observed as a miRNA inhibitor [43]. Additionally, circNT5E acts as a sponge that directly binds miR-422a and inhibits miR-42an activity, regulating multiple pathologic processes, including cell proliferation, migration and invasion in glioblastoma tumorigenesis [14]. Although circRNAs are generally expressed in small quantities, numerous studies have shown that circRNAs

are responsible for physiological development and different diseases, such as cardiovascular diseases [44–47], neurological disorders [20, 48, 49], and tumors [50–52]. Currently, circRNAs have also been reported to be enriched and stable in saliva [53], plasma [54], and even in serum exosomes [4], suggesting the potential of circRNAs as responsive biomarkers.

Origin of exosomal circRNAs

Generally, almost all cell types release exosomes that are enriched in plasma as well as other bodily fluids, including saliva, urine, semen, sputum and breast milk. Exosomes are also generated by both immune and nonimmune cells that have a significant role in the regulation of immunity [55]. Moreover, exosome release has been suggested to have prognostic relevance; increased levels of serum exosomes typically predicts unfavorable outcomes [56, 57]. Notably, Li first reported the enrichment and stability of abundant circRNAs in exosomes compared to the producer cells by using RNA-sequence analyses [58]. Although research on exosomal circRNAs is currently gaining momentum, the functions and characteristics of exosomal circRNAs remain largely unclear.

The composition of exosomal circRNAs may be modulated by changes in associated miRNA levels in donor cells, and subsequently this molecular information is transferred to recipient cells. In serum exosomes, circRNAs also contribute to the onset and progression of many neoplasias through RNA-RNA competitive interactions. For instance, circHIPK3 and TUG1 were upregulated, while LncRNA UCA1 was downregulated via RNA silencing, mitogen-activated protein kinase (MAPK) inhibition and in silico analyses [59]. Studies have shown that circRNAs are distinctly downregulated in a KRAS mutant and can be transferred to the exosomes of colorectal cancer cell lines [60]. Currently, exosomal circ-PDE8A was reported to be associated with tumor progression and lymphatic invasion by the miR-338/MACC1/MET pathway in pancreatic ductal adenocarcinoma [61]. Moreover, exosomal circRNA has been observed to promote white adipose browning via targeting the miR-133/PRDM16 pathway, providing a novel perspective into our understanding of cancer-associated cachexia [62]. Additionally, exosomal circRNAs originate from endometrial cancer and hepatocellular carcinoma by targeting the deubiquitination-related USP7, promoting tumor growth [63].

Apart from cancer origin, exosomal circRNAs commonly originate from activated human platelets, which are associated more with hemostasis, inflammation and wound healing than other hematopoietic cells [29, 64, 65]. Interestingly, Zhao showed that exosomal circRNAs might be responsible for the growth and repair of neurons, the transmission of nerve signals, and the regulation of important signaling pathways, specifically in glutamatergic synapses and the cGMP-PKG signaling pathway [66] (Fig. 1). Consequently, further research on exosomal circRNAs not only has profound impacts on understanding the functions and characteristics of exosomes but also provides a novel avenue for many disease diagnoses and targeted Therapies.
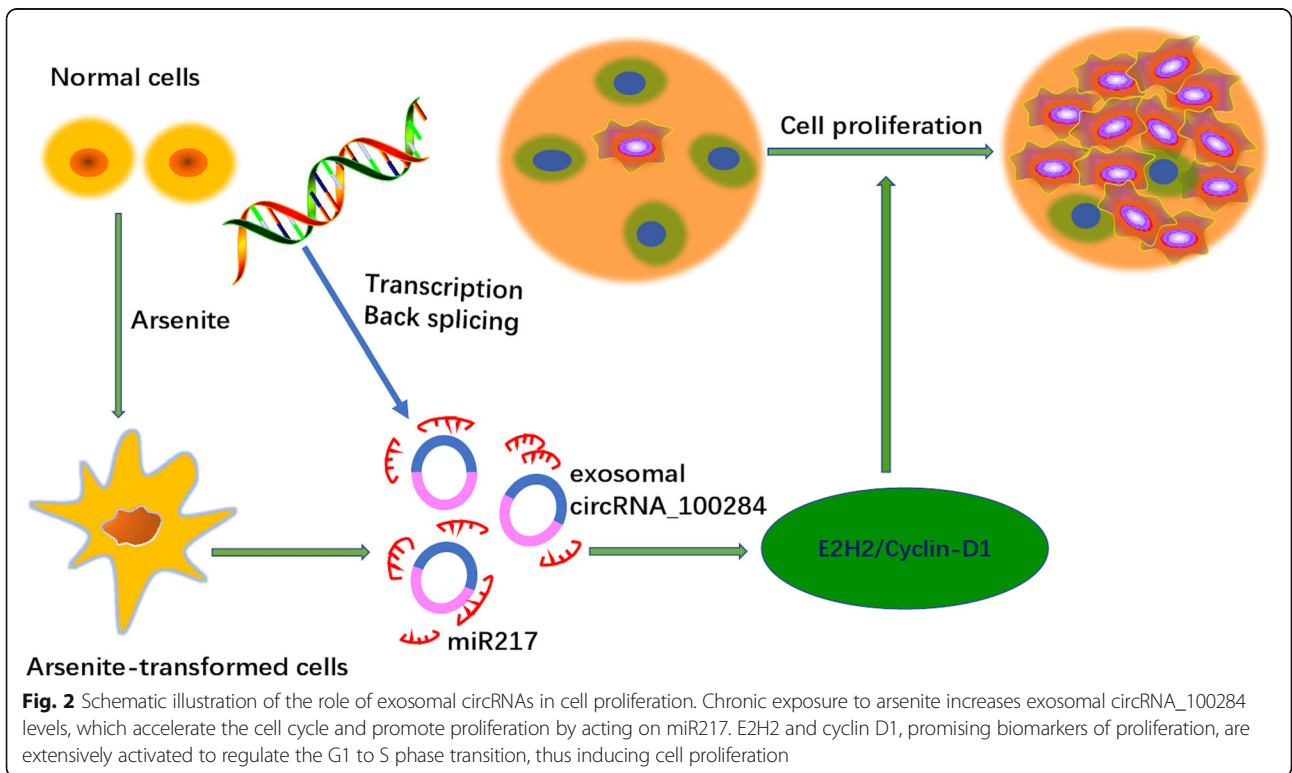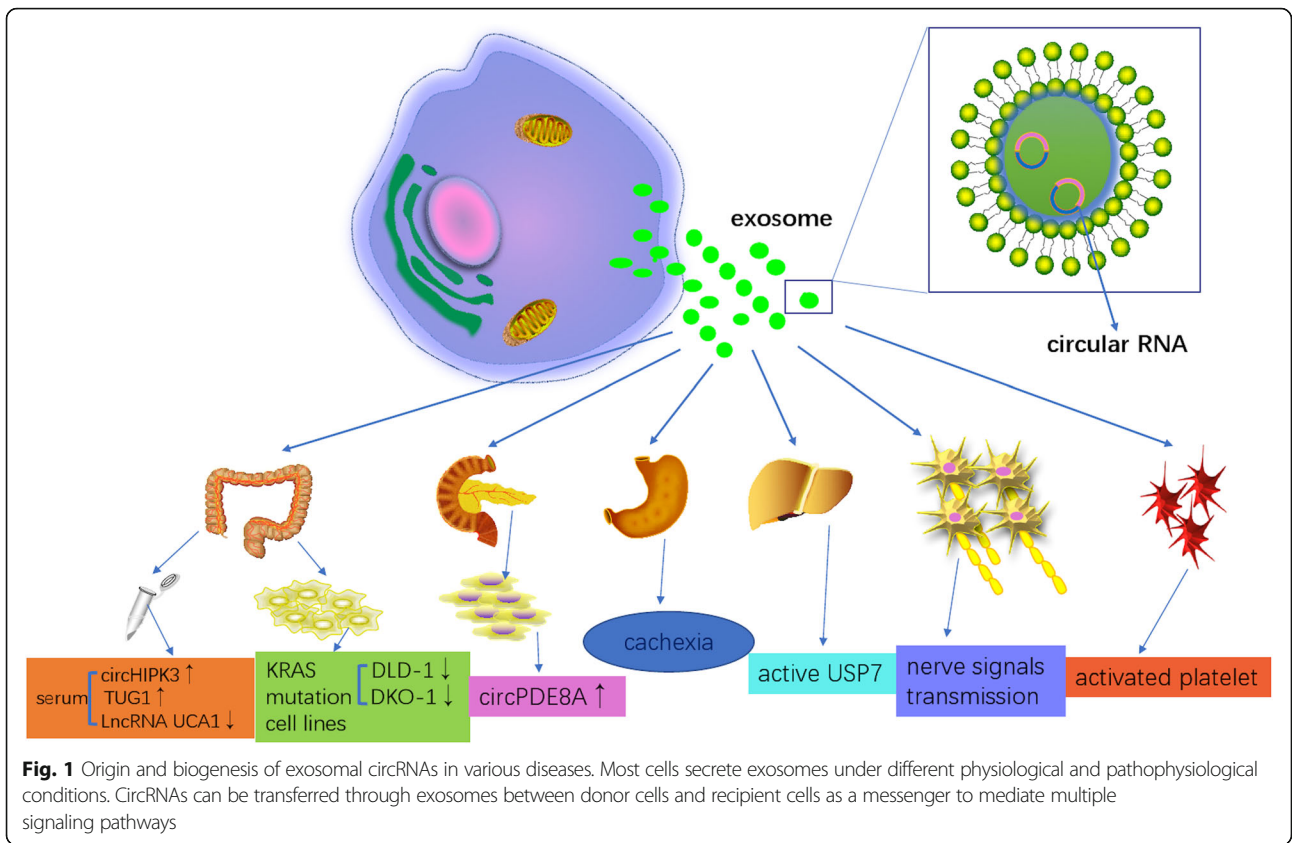
Biological functions of exosomal circRNAs

Exosome plays a key factor in the formation of premetastatic niches [67] and tumor microenvironment [68]. Additionally, exosomes have been found to associated with tumor cell survival and tumor recurrence through mediating immune suppression and immune surveillance [69, 70]. Interestingly, some circRNAs can be detected in exosomes derived from serum, urine and tumor, exosomal circRNAs may participate in the processes of cell growth, angiogenesis, epithelial mesenchymal transition, and targeted therapy. In this section, we focus on the essential roles of exosomal circRNAs in cell proliferation, tumor metastasis, and drug resistance.

Exosomal circRNAs and proliferation

Deregulated proliferation is one of the most important factors in neoplastic transformation; thus, increasing attention has been given to the understanding of the mechanisms of cell cycle regulation [71]. In previous reports, miRNAs were associated with the regulation of the cell cycle and the proliferation of hepatocellular carcinoma (HCC) cells [72, 73]. Interestingly, for arsenite-transformed HaCat cells, Dai reported that exosomal circRNA_100284 regulates the cell cycle by acting as a sponge of miR-217 [74] and inhibits cell proliferation by inducing arrest in the G2/M phase of the cell cycle and targets EZH2 in various cancers [75, 76], including HCCs [77, 78]. However, the underlying mechanisms of the regulation of EZH2 via miR-217 and how it affects malignant transformation still require further characterization.

Notably, recent studies have shown that the levels of circRNAs were increased in exosomes secreted from arsenite-transformed cells. The overexpression of miR-217 in normal cells reduced the expression of EZH2 (a promising biomarker of proliferation) [79, 80] and clclin-D1, which regulates the G1 to S phase transition in the cell cycle [81] (Fig. 2). This evidence suggests that exosomal circRNAs induced an accelerated cell cycle and promoted the proliferation of normal cells. Additionally, exosomal circRNAs secreted from adipose tissues can regulate the deubiquitination in HCC. Moreover, studies in vivo proved that overexpressed circ-deubiquitination (circ-DB) significantly downregulated miR-34a, leading to the activation of miR-34a/USP7/CyclinA2 signaling pathway. Consequently, exosomal circRNAs promote cell growth and suppress damage to DNA [63].
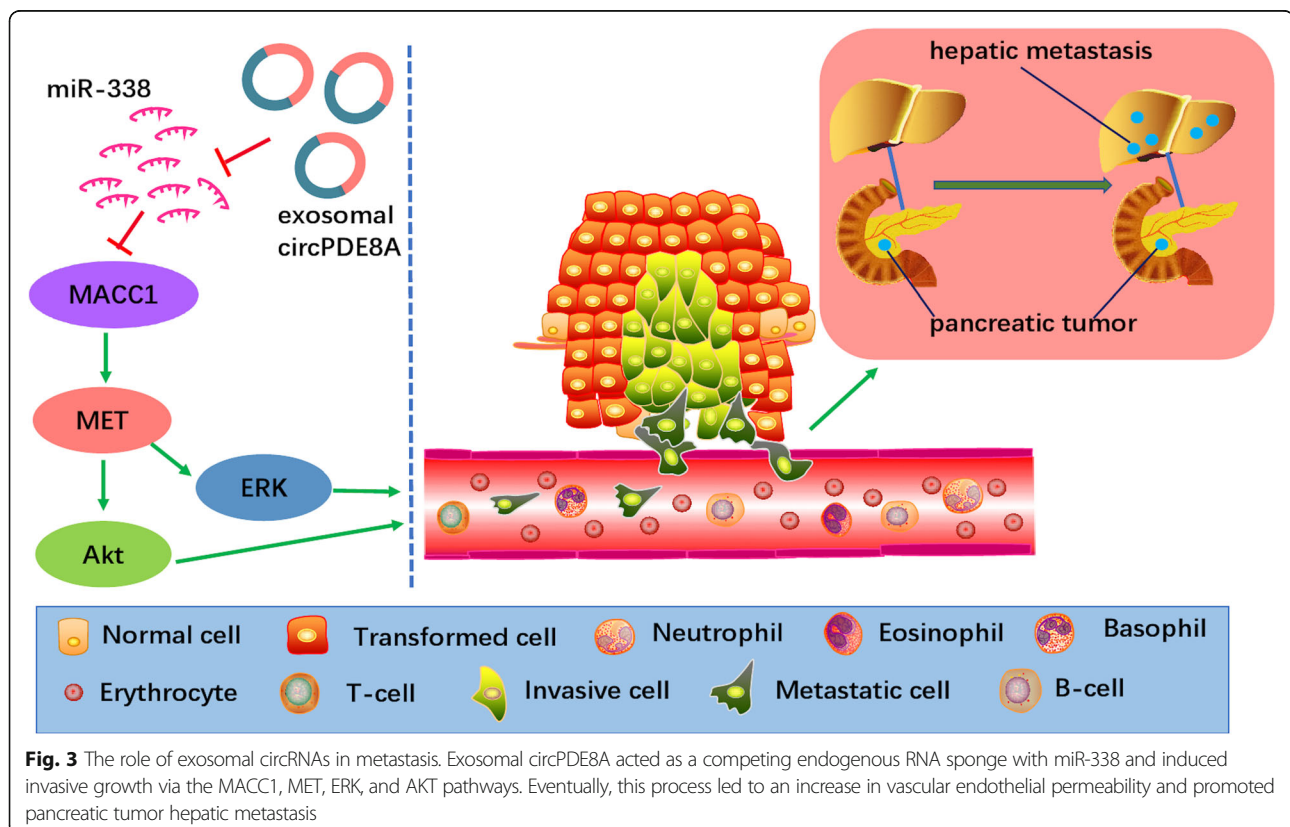
Fig. 1 Origin and biogenesis of exosomal circRNAs in various diseases. Most cells secrete exosomes under different physiological and pathophysiological conditions. CircRNAs can be transferred through exosomes between donor cells and recipient cells as a messenger to mediate multiple signaling pathways

Fig. 2 Schematic illustration of the role of exosomal circRNAs in cell proliferation. Chronic exposure to arsenite increases exosomal circRNA_100284 levels, which accelerate the cell cycle and promote proliferation by acting on miR217. E2H2 and cyclin D1, promising biomarkers of proliferation, are extensively activated to regulate the G1 to S phase transition, thus inducing cell proliferation

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Intriguingly, a recent study demonstrated that exosomal circRASSF2 promoted laryngeal squamous cell carcinoma (LSCC) progression. Researchers have found circRASSF2 expression was significantly and consistently increased in LSCC tumor tissues compared with control groups [82]. Moreover, they knockdown exosomal circRASSF2 remarkably inhibited cell proliferation and migration via miR-302b-3p/IGF-1R axis, indicating the significance of exosomal circRNAs in tumor cell proliferation.

Exosomal circRNAs and metastasis

Overwhelming studies conformed that tumor onset and metastasis are associated with many oncogenes and that many oncogenic pathways are involved [83]. Nowadays, growing evidences indicate that cancer cell-to-cell communication and surrounding stroma contribute to metastasis. For example, Li et al. first identified that an important role of exosomal circ-PED8A in pancreatic ductal adenocarcinoma (PDAC). They found that a high expression of exosomal circ-PED8A in PDAC tissue was associated with lymphatic invasion, TNM stage and a poor survival rate. Further research revealed that circ-PDE8A promoted tumore cells growth via upregulating MET, which is a tyrosine kinase receptor, one of the key oncogenes for a subset of epithelial tumors, including PDAC [84]. Moreover, tumor-excreted circ-PDE8A could be released into blood

circulation by exosome transportation, acting as a ceRNA for miR-338 to regulate MACC1 and promote invasive metastasis through the MACC/MET/ERK or AKT pathways (Fig. 3). Similarly, a recent study confirmed that circNRIP1 could be transmitted by exosome connection between gastric cancer (GC) cells, and exosomal circNRIP1 sponges miR-149-5p to affect the AKT1/mTOR signaling pathway and to promote the proliferation, migration and metastasis in gastric cancer [85]. Similarly, this phenomenon was also identified in breast cancer cells and patients [86]. These novel findings indicated the significance role of exosomal circRNAs in tumor metastasis.

Apart from the mentioned above, emerging evidence shows that the expression of certain exosomal circRNAs play important roles in the progression and metastasis of Hepatocellular carcinoma (HCC). For instance, Wang recently proved that exosomal circPTGR1 contributes to hepatocellular carcinoma metastasis [87]. Researchers found the high expression of exosomal circPTGR1 was related to the clinical stage and prognosis. In further, knockdown of exosomal circPTGR1 expression significantly suppressed tumor invasion and migration in non- and low-metastatic cell lines. According to bioinformatics analysis and both in vivo and in vitro experiments, exosomal circPTGR1 competed with MET interactions to target miR449a, leading to the dysregulation of tumor microenvironment and the promotion of HCC development.

Fig. 3 The role of exosomal circRNAs in metastasis. Exosomal circPDE8A acted as a competing endogenous RNA sponge with miR-338 and induced invasive growth via the MACC1, MET, ERK, and AKT pathways. Eventually, this process led to an increase in vascular endothelial permeability and promoted pancreatic tumor hepatic metastasis

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Pathological epithelial mesenchymal transition (EMT) plays essential roles in tumor progression and the initiation of metastasis. Recently, Jie found that circ-IARS, secreted by pancreatic cancer cells and located in exosomes, was extensively expressed in pancreatic cancer tissues, and its expression level was responsible for tumor vasculature, tumor node metastasis (TNM) stage and liver metastasis [31]. Cancer cells must cross the endothelial barrier during extravasation for tumor distant metastasis [88]. Interestingly, the Ras homolog gene family, member A (RhoA), is associated with cytoskeleton regulation and reduces the expression of the junction ligand protein Zonula occludens-1 (ZO-1), leading to endothelial barrier dysfunction and endothelial solute permeability [89–91]. It was indicated that the tumor suppressor miR-122 incudes mesenchymal-epithelial transition and inhibits the migration and metastasis of HCC by targeting RhoA [92]. Moreover, increased activity and expression of RhoA in human microvascular vein endothelial cells (HUVECs) was recently indicated to increase F-actin expression and decrease ZO-1 [93, 94], which damages the endothelial barrier function [89–91] and reinforces endothelial permeability [95–99]. In addition, Chen X et al. revealed that circPRMT5 was upregulated in serum and urine exosomes from urothelial carcinoma of the bladder (UCB) tissues [100]. Further study confirmed exosomal circPRMT5 promoted UCB cell EMT via blocking with miR-30c, leading to the high expression of SNAIL1 and E-cadherin. Consequently, circRNAs can be transferred through exosomes from cancer cells to other cells as messengers, mediating cell-to-cell communication, regulating endothelial permeability, and thus promoting tumor metastasis.

Exosomal circRNAs and drug resistance
Drug resistance is considered an enormous impediment in the treatment of cancer patients. As various underlying mechanisms are related to the progression of drug resistance, exosomes have attracted and gained universal attention as a novel therapeutic avenue [101, 102]. Importantly, exosomes transmit multi-drug resistance (MDR)-associated proteins [103] and noncoding RNAs to target cells [104], including circRNAs. For instance, Li L. et al. currently revealed serum exosomal circRNA (FECR1) was aberrantly upregulated in small cell lung cancer (SCLC) compared with control groups. In addition, serum exosomal- FECR1 was asscociated with clinical chemotherapy and poor survival in SCLC patients [105]. These evidences suggested a possible relationship between exosomal circRNAs dysregulation and drug resistance.

Accumulating evidence has shown that epithelial cancers, such as colorectal cancer (CRC), are preferentially resistant to many advanced drug therapies. Epidermal growth factor receptor (EGFR), a member of the HER-ErbB family, plays a significant role in the proliferation, angiogenesis, gene mutation and drug resistance in CRC. KRAS is an intracellular signaling molecule, and its mutations are found in approximately 40% of colorectal tumors [106]. Therefore, the identification of the key signaling pathways impacted by the KRAS mutation is beneficial for our understanding of how to pharmacologically target therapies.

Interestingly, the abundance of circRTN4 was remarkably upregulated in the exosomes derived from DLD-1 CRC cells, which possess a KRAS mutation compared with DKs-8 cells (wild-type KRAS). However, the intracellular abundance of circRTN4 was significantly downregulated in DLD-1 and DKO-1 cells, indicating exosomal circRNAs are independent of intracellular circRNA and may be actively transmitted between exosomes and the cytoplasm [60, 107]. These findings provide new insight into the function of exosomal circRNAs and demonstrate their ability to regulate chemotherapy resistance.

Clinical applications
The nascent era of the clinical application of exosomel circRNA is growing rapidly. Emerging evidences suggest that exosomal circRNAs are released from various cells and carry signaling molecules for cellular communication, even the regulation of organ function. In addition, the expression profiles of exosomal circRNAs in patients distinguish from healthy groups, it is possible that exosomal circRNAs can function as molecular markers of some tumors to support diagnosis. Exosomal circRNAs are also being recognized as crucial mediators of healthy and diseased states and may become promising biomarkers of specific conditions. For instance, the levels of exosomal circRNAs were significantly up-regulated in DKs-8 cells compared to DLD-1 and DKO-1cells [60], suggesting that exosomal circRNAs may serve as a promising biomarker in colon cancers. Similarly, exosomal circular RNA IARS expression was higher than those of control groups both in pancreatic cancer tissues and in plasma exosomes [31], the result of this study indicated that the existence of exosomal circRNA could be a useful marker of PDAC diagnosis and prognostic prediction.

In addition, exosome-derived miRNA and proteomic materials may be used as diagnostic indicators of various tumors, such as ovarian, prostate and lung cancer [108–110]. Unlike miRNA, circRNAs are exceptionally stable, conserved and have cell–/tissue-specific expression patterns, which suggest their potential applications as gene regulators as well as their possibility as molecular diagnostic and prognostic biomarkers. Importantly, the unique cellular stability and function of circRNAs to sponge miRNA and proteins may also indicate that

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circRNA is a promising vehicle for targeted drug delivery [111]. Despite its large potential, our understanding of exosomal circRNA is still in infancy.

Intriguingly, according to Li, 1215 circRNAs were identified in the human serum exosomes, and more than 90% of the detected circRNAs consisted of exons showed high stability and conserved exonuclease cleavage, suggesting that circRNAs can be actively transferred from cells to exosomes and indicating the underlying possibility of tumor diagnostic markers. Due to their applicability, specificity and accessibility, exosomal circRNAs have the potential for cellular therapy and for the theoretical concerns of neoplastic transformation from peripheric blood-, tissue-, or bone marrow derived stem cell transplantation.

Conclusions and perspectives

Exosomal circRNAs are a novel frontier in cancer research, and only a few of circRNAs have established functional roles or clinical applications. Exosomal circRNAs modulate cellular proliferation, invasion, migration, metastasis and drug resistance. In addition, exploring the mysterious connection of exosome and circRNA may provide a vital hint to understand the biological functions of exosomal circRNAs. Currently, there are two assumptions of circRNA in exosomes. Interestingly, exosome might be a double-edged sword for circRNA. One is that exosome is a communication messenger between cells due to its accessibility in bodily fluids. Exosome can carry circRNA to transfer biological information and material to target cells and protect circRNA from clearance. The other is that exosome could reduce the accumulation of circRNAs and help circRNA clearance. Erika Lasda point out that cells can eliminate circRNA by excreting them via extracellular vesicles [32], which could be taken up by other specific cells, including macrophages.

Despite the abovementioned encouraging advances, challenges and difficulties of exosomal circRNAs in clinical applications exist in multiple aspects. First, due to their low abundance, circRNAs are difficult to be detected in exosomes with an accurate approach and algorithms. Second, the circular conformation and sequence overlap with linear mRNA counterparts have made the precise evaluation of circRNA expression and function challenging. It is worthy nothing that these problems will be solved with the advanced technology, improved experimental approaches and further research.

Recent studies have indicated that exosomal circRNAs may have a significant influence on pathophysiologic processes. The connection of exosomal circRNAs with cancer has become a popular research field. However, there are still some questions that need to be addressed. First, we lack an understanding of how circRNAs are ultimately degraded. In addition, the mechanism of how circRNAs are enriched during exosome formation is unknown. One possibility is that circRNAs are abundant in the cytoplasm and passively included in exosomes during their formation. Alternatively, circRNAs may be actively transferred from the cytoplasm into exosomes. Future studies investigating exosomal circRNAs in the hematopoietic system, immune response, nervous disorders, cancer development and other biological settings and diseases will further unveil the mystery of exosomal circRNAs. Therefore, revealing cancer pathogenesis mechanisms and seeking novel potential diagnostic biomarkers or therapeutic targets will be popular topics in the future.

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