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Review

Tumor Cells-derived exosomal CircRNAs: Novel cancer drivers, molecular mechanisms, and clinical opportunities

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ABSTRACT

Recently, circular RNAs (circRNAs) have appealed to a growing interest due to their abundant expression and potential functions in cancer development. The most biological function of circRNAs may include acting as a sponge for miRNAs and proteins in different physio/pathological conditions. CircRNAs promote cancer progression by regulating several procedures such as growth, invasion, metastasis, angiogenesis, and drug resistance. Emerging evidence has shown that circRNAs frequently have tumor-specific expression, proposing these molecules serve as diagnostic and prognostic cancer biomarkers. Furthermore, circRNAs may be used as a potential target for the treatment of cancers as they can sponge oncogenic miRNAs and proteins. Exosomes, a subtype of extracellular vesicles mediate intercellular communication, contain circRNAs and deliver them to target cells inducing cancer development through different signaling pathways. Exosomal circRNAs may serve as a diagnostic and prognostic biomarker for cancers. Targeting exosomes may represent novel approaches for the treatment of cancers through using them as cell-free therapy and drug-delivery system and inhibiting their biogenesis and distribution. However, research on circRNAs biology is advancing and some concerns such as technical issues in the characterization and analysis of circRNAs along with biological understanding gaps necessary to be considered to transfer this undeveloped field to the vanguard of clinical studies. In this review, we discuss the existing information on the formation of circRNA and its roles in the tumor as a biomarker and treatment target. Furthermore, we describe tumor-derived exosomes enclosed circRNAs and their possible roles in cancer development and their potential as biomarkers and therapeutic approaches.

1. Introduction

Cancer, the main second reason for mortality globally, is well-known as a multifactorial disease that originated from the continuous increase of epigenetic and genetic modifications in genes coding proteins [1]. In past decades, detailed scrutiny fcancer-associated proteins has confirmed that specific protein abnormalities are associated with the acquisition of cancer and facilitated the progress of targeted therapies for previously intractable cancers. The finding that over seventy percent of the human genome is transcribed to produce considerably noncoding RNAs (ncRNAs) has changed our opinion of the functional genomic area [2,3]. NcRNAs are produced from the larger part of the genome that does not encode proteins but yields noncoding transcript copies that control different genes expression and protein functions [4,5]. Gene expression profiling has shown that different ncRNAs like microRNAs (miRs), long noncoding RNAs (lncRNAs), and circular RNAs (circRNAs) are frequently differentially regulated in tumor cells and biopsy samples of cancer patients compared to normal ones [6]. We describe mechanisms involved in circRNAs formation and their role in tumorigenesis. Recent evidence suggests that many various genes yield extremely conserved, firm, and locked RNA circles regulating many genes. Recent trends in circRNAs biology showed that these RNAs are significant

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factors in cellular physiology, tissue homeostasis, and also in disease progress [4,7,8]. It seems that the expression of circRNAs is frequently separate from the linear expression pattern of the host gene. This discusses that circRNAs are generated by an unconventional splicing mechanism, which is dissimilar to the common mRNA splicing mechanism [4]. CircRNAs are proposed to be downregulated in tumor mass where the proliferation of cells is high, probably because of the sharing of these molecules in newly formed cells before reaching stable state stages [9,10]. Recent studies have confirmed that cancer cells release extracellular vesicles (EVs) such as exosomes, which transfer many kinds of circRNAs to recipient cells and participate in tumorigenesis [11,12]. Many body fluids contain exosomes that make them ideal for non-invasive ways to monitor cancers as biomarkers. At present, we discuss the last knowledge on circRNAs biogenesis and their key role of them in cancer development. In addition, we describe recent progress in discovering exosomal circRNAs in cancer development. Finally, we also describe circRNA promising biomarker potential for cancer diagnosis, prognosis, and therapeutic targets in the prospect of personalized medicine.

2. CircRNAs biogenesis

For the first time, circRNAs have discovered approximately 43 years ago [13], then it was suggested that mis-splicing yields circRNAs molecules [14] and were commonly reflected particularities of indefinite biological significance. Only circRNAs molecules from the sex-determining region Y (Sry) gene were believed to act functionally [15]. The detailed mechanistic pathway involved in circRNA biogenesis is not fully understood. There are some reasons why circRNA waited in the obscurities for so several years. circRNAs are not detectable through many traditional techniques. Conventional qPCR analysis cannot discriminate circRNAs from mRNAs when the linear genome is used as a pattern for designing certain primers [4,16]. Moreover, circRNAs do have no poly (A) tails, therefore they can easily escape from detectable methods because most methods used for the RNA sequencing library use a poly (A) isolation phase to eliminate rRNA. Recent advancements in RNA sequencing methods and bioinformatics systems have led to finding thousands of circRNAs molecules in different eukaryotes like mammals, plants, insects, fungi, worms, and fish [17,18]. Despite the absence of capping and poly(A), circRNAs are commonly resident in the cytoplasm [19,20]. These molecules can up-regulate the expression of original genes in cooperation with the U1 small nuclear ribonucleoprotein (snRNP) for example circPAIP2 and circEIF3J [5] or by activation of transcription activity of RNA polymerase II (Pol II) like ci-ankrd52 [21]. Two mechanisms may be involved in circRNAs biogenesis. As shown by Fig. 1, one is the back-splicing mechanism that the 3′-end of an exon link to an upstream 5′-end covalently resulting in the construction of a circRNA, which is mediated by reverse complementary *Alu* regions neighboring the geniculated exon [21,22]. In addition, splicing factors may regulate the back-splicing process by interaction with the *cis*-acting splicing regulatory element (SRE), which stables circularization [19,23]. The exon-skipping mechanism is another way to generate circRNAs molecules where an exon-containing lariat ancestor is formed. This lariat is internally spliced where the intronic sequence is being removed, therefore circRNAs are generated [20] (Fig. 1). Once formed, the majority of circRNAs are transferred to the cytoplasm. Spliceosome RNA helicase DDX39B and ATP-dependent RNA helicase DDX39A mediate exporting these molecules from the nucleus to the cytoplasm in a size-dependent way [24]. Some transacting RNA-binding proteins (RBPs) may contribute to circRNA biogenesis including call quaking (QKI), ADAR, FUS, DHX9, and HNRNPL that regulate several but not all circRNAs [5,21,25,26]. Among them, DHX9 may be a therapeutic target for some cancers [27]. In addition, QKI is suggested as a new tumor suppressor factor in lung tumor and has prognosis potential [28,29].

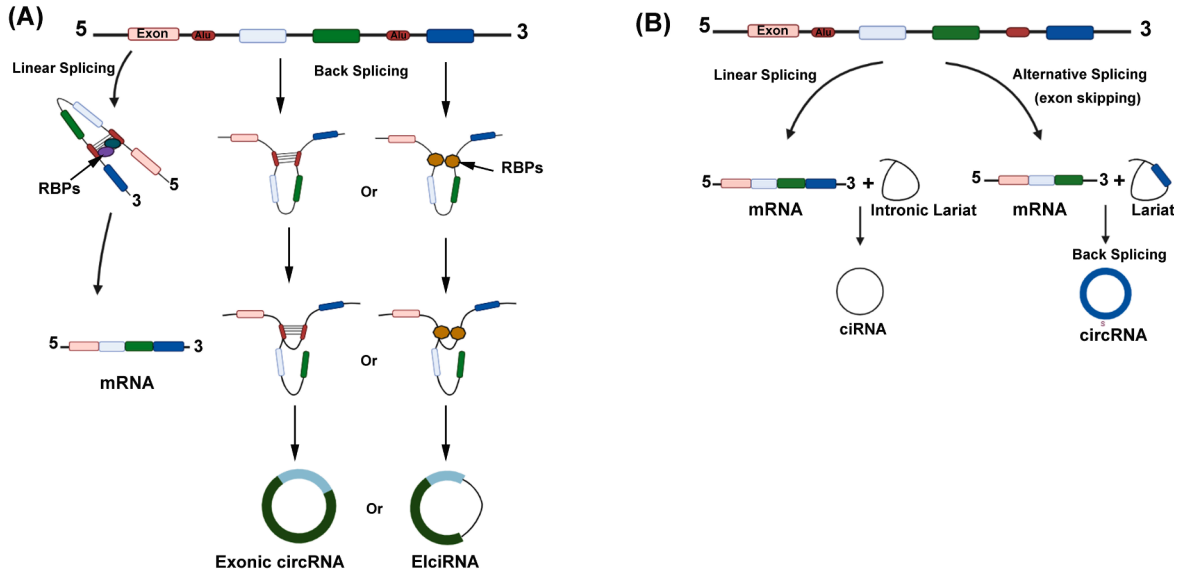

Fig. 1. CircRNAs biogenesis. Either linear RNAs or circRNAs are formed from pre-mRNAs, however, counter to linear RNAs that are generated through conventional splicing, circRNAs are typically made by back-splicing. CircRNAs may be generated from most parts of the genome, such as intronic, intergenic, untranslational regions, and antisense. Based on their origin, three major classes of circRNAs can be generated as circular intronic RNAs (ciRNAs), exon–intron circRNAs (EIciRNAs), and exonic circRNAs (ecircRNAs). Some of circRNAs may be generated by a mechanism called exon skipping process. The majority part of circRNAs is EcircRNAs that formed from exons. In brief, two mechanisms of circRNAs biogenesis have been suggested. (A) Intron pairing-driven circularizing mechanism where EIcircRNAs or exonic circRNAs are being formed. In this mechanism, complementary sequences or specific *trans*-acting RNA binding proteins (RBPs) mediate the formation of the circular structure by base-pairing modus through exon-flanking introns. Intron paring interacts with the splice positions nearby each other where exon circularization occurs by back-splicing of pre-mRNAs. In contrast, conventional linear splicing (right) is facilitated by exons enclosed by short flanking introns. Certain RBPs such as ATP dependent RNA helicase A (DHX9) and double-stranded RNA-specific adenosine deaminase (ADAR1) interrupt base pairing between Alu elements, resulting in the formation of linear mRNA. (B) circRNAs can be formed by the second mechanism known Iariat-driven circularization mechanism where the introns in a lariat intermediate that contains different introns and exons are detached. By linear splicing, intronic lariat precursors may evade the debranching phase (left) or an exon-skipping process occurs for the duration of linear splicing (right).

Though back-splicing is commonly less effective than linear splicing, circRNAs may temporally mount up in particular cells [26,30] because of their high stability [31], which may seemingly raise from their covalently closed circular configuration shielding circRNAs from degradation [31]. These molecules are usually expressed at lower levels than their linear equals although circRNAs are the principal transcript for many genes [27,29], and competitiveness between back-splicing and canonical splicing is possible to happen for most loci that yield circRNAs [20]. CircRNAs are very stable molecules and their turnover is complex and underlying mechanisms are also not well-known. These molecules are more stable due to the closed free ends, which make these molecules impervious to exonucleolytic degradation. However, circRNAs may have particular endonuclease locations that possibly will be cleaved in a regulated pathway. For example, miR-671 may bind to a highly complementary location and initiate cleavage of the ciRS-7 molecule through Ago2 protein [32,33]. Although our knowledge of mechanisms overriding the expression of circRNAs as important biomolecules is insufficient yet, many researchers have shown that these molecules are deregulated in various human cancers not only in solid tumors like liver, colorectal, prostate, lung, breast, ovarian, bladder, gastric, and kidney cancer but also in hematological cancer and malignant tumor of the central nervous system. Therefore, it seems that circRNAs are vital players in tumorigenesis, and they may impact numerous of the hallmarks of malignancies [34].

3. Biological functions of circRNAs

Although up to 100,000 circRNAs have been identified in human cells [35,36], these molecules are still being compared to other transcript molecules. The third locus of codons is highly conserved in several circRNAs compared to exons that are included in circRNAs [19], proposing that circRNAs play a key non-coding role that may mirror their great stability. In addition, circRNAs have internal ribosome entry site (IRES) components and AUG positions, suggesting an indication for their translation [14]. According to previous studies, some circRNAs can translate in cells under certain situations [37,38], but especially in cancer. Because of the considerably longer half-life, circRNAs may have different functions that we summarized in Fig. 2. Several roles have been proposed for circRNAs, for example, most of the circRNAs act as miRNA sponges [39,40] (Fig. 2a) or they may interact with many several RBPs [41] to sponge specific proteins [42] (Fig. 2b). In addition, they may improve protein function [5,21] (Fig. 2c) or serve as scaffolds to facilitate complex development between substrates and enzymes [43] (Fig. 3d) or participate in trafficking proteins to specific positions [44] (Fig. 3e). Besides, certain circRNAs may be translated into peptides in a cap-independent mode under particular conditions [45–47] (Fig. 3f), while most circRNAs are believed to be non-coding molecules. Some circRNAs contribute to cancer development through different pathways including, promoting cell proliferation, inducing epithelial to mesenchyme transition (EMT) and metastasis, evading apoptosis, increasing angiogenesis, and inducing stemness and chemotherapy resistance. We summarized the biological roles of key circRNAs with a focus on cancer in Table 1.

4. The role of circRNAs in cancer

CircRNAs can participate in cancer progression through several roles have been presented in Fig. 2. For instance, Foxo3 has been shown to play as protein scaffolds for mouse double-minute 2 (MDM2) and p53, inducing tumor apoptosis [48]. We summarized the pivotal role of circRNAs in cancers in Table 1. In keeping, we describe circRNAs enclosed in extracellular vesicles especially those derived from cancer cells.

4.1. CircRNAs as miRNA sponges in cancer

The key role of circRNAs in cancer is acting as a miRNA sponge. For example, CDR1as/ciRS-7 is a miRNA-7 sponge that has more than 70 binding sites for miR-7 [49]. MiR-7 is a tumor suppressor factor in many cancers, like gastric cancer (GC)[50], colorectal cancer (CRC)[51], cervical cancer [52], breast cancer [53], lung neoplasm [54], Schwannoma tumor [55], hepatocellular carcinoma (HCC)[56], and tongue cancer [57]. CiRS-7 can up-regulate genes targeted by miR-7, therefore inhibiting the tumor suppression genes, and increasing lung cancer development [58]. In cancer cells, miR-7 contribute to inhibition of various pathways, including oncogenic protein epidermal growth factor receptor (EGFR)[59], Yin Yang 1 (YY1)[51], mammalian target of rapamycin (mTOR)[56], insulin receptor substrate-1- and 2 (IRS-1 and

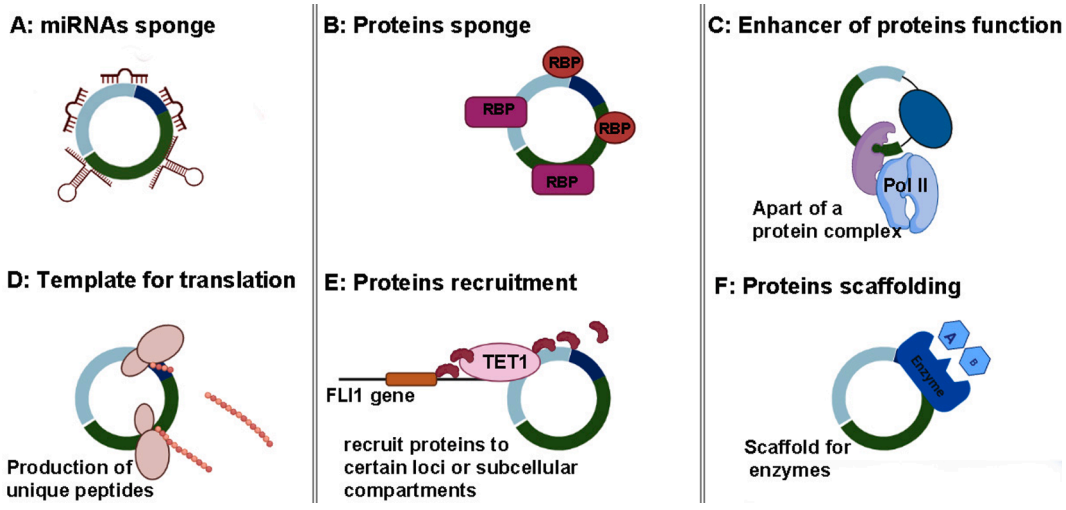

Fig. 2. Roles of circRNAs in cancer. Most of circRNAs may act as miRNA sponges, shielding target mRNAs from silencing (A). CircRNAs also may act as proteins sponges. Certain circRNAs have RNA binding protein (RBP) binding sites that bind proteins and control their functions indirectly (B). CircRNAs may increase the function of specific proteins. For example, circRNAs may promote the activity of the RNA polymerase II (Pol II) complex enclosing the U1 small nuclear ribonucleoprotein (snRNP) and different proteins (C). Under certain conditions, circRNAs containing AUG sites and internal ribosome entry site (IRES) elements could be translated into some unique peptides (D). CircRNAs are proposed that employ particular elements to specific loci or subcellular parts, here for example, for the FLI1 gene which use TET1 to the promoter area of its gene (E). Some circRNAs may serve as protein scaffolds for enzymes and substrates, expediting the reaction kinetics (F).

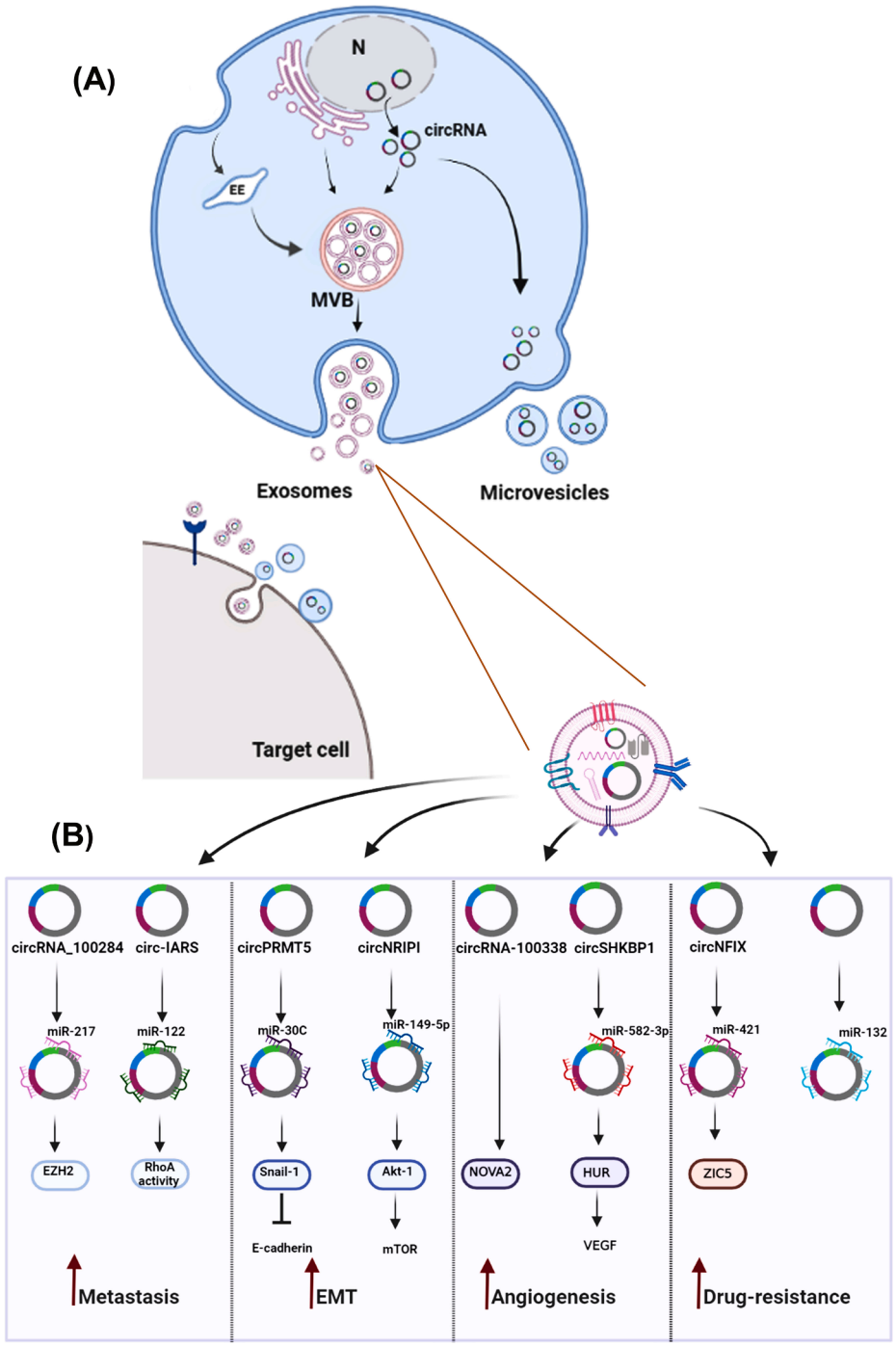

Fig. 3. Biogenesis of exosomes and microvesicles from cells. Extracellular vesicles (EVs) such as exosomes and microvesicles (EVs) are generated from the multivesicular body (MVB) and the plasma membrane shedding mechanism respectively. CircRNAs are generated in the nucleus and transported into the cytoplasm. These molecules can be sorted into MVBs/exosomes and MVs via certain pathways and delivered to other cells. Once secreted, EVs distribute into extracellular fluids and reach target cells and regulate different signaling pathways. the lower section illustrates the pivotal role of the key exosomal circRNAs in cancer development through increasing metastasis, epithelial-mesenchymal-transition (EMT) process, angiogenesis, and drug resistance. EE: early endosome.

IRS-2)[59], P21-activated kinase-1 (Pak1)[60], Raf1[61], phosphoinositide 3-kinase catalytic subunit delta (PIK3CD) [61], PA28γ [62], and Ack1 [55]. Furthermore, miR-7 may indirectly inhibit signal STAT3 by inhibiting histone-lysine N-methyltransferase1 (SETDB1), which induces EMT phenotype, therefore inhibiting the invasion and metastasis rate of breast tumor cells [53]. It was demonstrated that miR-7 can reduce the expression of p65, which in turn activates NF-κB causing inhibition in HCC invasion [63]. On contrary, some researchers declared that miR-7 can promote tumorigenesis. For instance, in the HPV-positive HeLa cell line, Honegger *et al.* showed that E6/E7 as a viral oncogene is associated with miR-7 overexpression [64] and a study by Nakagawa and co-workers showed that miR-7 is highly expressed in CRCs [65]. It seems that circRNAs act as either tumor suppressors or promoters, which therefore depends on the expression level and type of miRs sponged by circRNAs. Similarly, in CRC, cir-ITCH can sponge miR-7 and miR-20a which suppress tumor cells proliferation through the Wnt/β-catenin pathway [66]. Similarly, cir-ITCH can sponge miR-17, miR-7, and miR-214, resulting in suppression of esophageal squamous cell carcinoma (ESCC) by the Wnt/β-catenin signaling [67], whereas cir-ITCH sponges miR-214 and miR-7 and suppresses lung cancer progress [68]. CircHIPK3 supports human cancer development by sponging and inhibiting miR-124 [40]. Foxo3 circular RNA (circ-Foxo3) up-regulates translation Foxo3 by inhibiting potential different miRNAs, therefore inhibiting tumor cell proliferation, tumor growth, and survival [69]. More recently, Qiu *et al.* found that circ_0000658 sponges miR-498 in bladder cancer cells, inducing EMT phonotype and tumorigenesis. They also

Table 1
The pivotal role of the key circRNAs in cancer progression.

Process	CircRNAs	Cancer	Regulation	target	Function in process	Ref.
Cell proliferation	hsa_circ_0046701	glioma	Up-regulated	miR-142-3p/ITGB8	increase	[136]
	circ-FBXW7	glioma	Down- regulated	FBXW7-185aa/c-Myc	Inhibit	[137]
	circ-DNMT1	BC	Up-regulated	AUF1, p53	increase	[138]
	circRNA-000425	GC	Down- regulated	miR-106,miR-17 /p21, BIM	Inhibit	[139]
	circHIPK3	CRC	Up-regulated	miR-7/ IGF1R, EGFR, YY1, FAK	Inhibit	[140]
	CDR1as	HCC	Down- regulated	miR-7/EGFR	Increase	[141]
	CDR1as	NSCLC	Up-regulated	miR-7/EGFR, PIK3CD, CCNE1	Increase	[142]
	CDR1as	GC	Up-regulated	miR-7/PTEN/PI3K/AKT	Increase	[143]
	circRNA-0002109	Glioma	Up-regulated	miR-129-5P/EMP2	Increase	[144]
	Circ100284	Melanoma	Up-regulated	miR-217/EZH2/ CDK4, cyclin D1	Increase	[145]
	circHIPK3	gallbladder cancer	Up-regulated	miR-124/ CDK6, ROCK1	Increase	[146]
	hsa_circ_0016788	HCC	Up-regulated	miR-486/CDK4	Increase	[147]
Apoptosis	circ-ITCH	Bladder Cancer	Down- regulated	miR-224, miR-17 /p21, PTEN	Increase	[148]
	circ-ZFR	GC	Down- regulated	miR-107, miR-130a/PTEN	Increase	[149]
	hsa_circ_0007534	CRC	Up-regulated	Bax, Bcl-2	Increase	[150]
	hsa_circRNA_103809	CRC	Down- regulated	miR-532-3p/FOXO4 pathway	Increase	[151]
	hsa_circ_0009910	osteosarcoma	Up-regulated	miR-449a/IL6R/Bcl-2/Bax	Inhibit	[152]
	circUBAP2	osteosarcoma	Up-regulated	miR-143/Bcl-2	Inhibit	[153]
	circNFIX	glima	Up-regulated	miR-34a-5p/NOTCH1	Inhibit	[154]
	has-circ-0020397	CRC	Up-regulated	mir-138/ PD-L1, TERT	Inhibit	[155]
EMT/Metastasis	circPTK2	NSCLC	Down- regulated	miR-200b-3p, miR-429 /TIF1y	Inhibit	[156]
	circ-10,720	HCC	Up-regulated	Vimentin	Increase	[157]
	circSMAD2	HCC	Down- regulated	miR-629	Inhibit	[158]
	circ_0067934	NSCLC	Up-regulated	E-cadherin, N-cadherin, snail, vimentin	Increase	[159]
	hsa_circ_0061140	ovarian cancer	Up-regulated	miR-370/FOXM1	Increase	[160]
	circRNA_0023642	GC	Up-regulated	E-cadherin, N-cadherin, snail, vimentin	Increase	[161]
Angiogenesis	circHIPK3	Bladder Cancer	Down- regulated	miR-558/ VEGF /HPSE	Inhibit	[162]
	circRNA-MYLK	Bladder Cancer	Up-regulated	miR-29a/VEGFA/VEGFR2	Increase	[22]
	cZNF292	Glima	Up-regulated	VEGF-A, TGF-β1EGF,	Increase	[23]
Drug- resistance	circBA9.3	CML	Up-regulated	c-ABL1 and BCR-ABL1	Increase	[163]
	hg19_circ_0005033	LSCC	Up-regulated	miR-4521	Increase	[164]
	hsa-circRNA-007874	BC	Up-regulated	TRAF4/Eg5 axis	Inhibit	[165]
	circPVT1	osteosarcoma	Up-regulated	ABCB1	Increase	[166]
	circVRK1	BC	Down- regulated	–	Increase	

showed that circ_0000658 /miR-498 caused an up-regulation in mRNA level of N-cadherin, ZEB1, Slug, Twist, and Snail as well as a decrease in the level of E-cadherin and β-catenin [70]. In breast cancer, it was reported that circRNA_1093, has four miR-342-3p binding sites, can regulate expression of BRCA1[71]. As the miR-200 sponge, such circRNAs as circZEB1.5, circ-ZEB1.19, circZEB-1.17, and circZEB1.33 are lowly expressed in the lung cancer [72]. Hsa_circ_001569 may sponge miR-145 and support proliferation and invasion of CRC. It impedes the transcriptional activity of miR-145, which induces an increase in miR-145 target genes like FMNL2, BAG4, and E2F5 [73]. A work indicated that circ-TTBK2, as miR-217 sponge, was increased in cell lines and glioma tissues and mediated tumorigenesis by miR-217/HNF1β/Derlin-1 pathway [74]. CircRNAs may target miRs involved in tumor angiogenesis. For example, in gliomas, circSCAF11 increased the expression of SP1 by sponging miR-421. In turn, SP1 facilitated expression of VEGF-A, thus, the circSCAF11/miR-421/SP1/VEGF-A axis participated in tumor angiogenesis [75]. In endothelial cells of glioma, circ-ATXN1 increases cell proliferation, invasion, and angiogenesis by targeting miR-526b-3p to increasing MMP2 and VEGFA levels [76]. Furthermore, Zhong *et al.* showed that circRNAsMYLK removed miR-29a in bladder cancer, which resulted in an activation in Ras/ERK and VEGFA/VEGFR2 signalings, and further induce metastasis and angiogenesis [77]. However, despite of many evidences, the detailed mechanisms involved in circRNA-miRNA-gene interaction requirements additional studies.

4.2. CircRNAs as transcription regulators in cancer

Some circRNAs such as ci-sirt7 and cimcm5 may participate in regulating the expression of their parental genes, which in turn can inhibit or support cancer development [21,78]. Overexpression of MCM5 is thought to deal with both oral squamous cell carcinoma and CRC, associated with poor prognosis [79,80]. In pancreatic ductal adenocarcinoma (PDAC), down-regulation of SIRT7 contributes to metastasis and poor value for prognosis [81]. Yang *et al.* revealed that cZNF292 inhibits the tubulogenesis potential of glioma cells by Wnt/β-catenin pathway and down-regulating Cyclin A, CDK2, p-STAT3, p-CDK2, and p-STAT5. They showed that inhibition of cZNF292 causes a decrease in the transcription level of NF-κB, E2F1, HIF-1, Sp1, STAT3, STAT5, and AP-1, preventing tumor cells tubulogenesis [82]. These results suggest that circRNAs may regulate genes and cancer progression.

4.3. CircRNAs as RBP sponges in cancer

As mentioned, some RBPs like MBL, QKI, Pol II, and AGO could interact with circRNAs. RBP-mediated regulation of genes either at transcription or expression levels plays an important role in cancer [83]. QKI-5 is a new tumor suppressor molecule in various tumors like prostate cancer and lung cancer [84,85]. CircRNAs generation is controlled by QKI, suggesting a new standpoint to QKI-related circRNAs targeting approaches in tumor. In addition, AGO proteins were frequently over-expressed in tumor cells and closely associated with the progress of cancer in miRNAs-dependent or independent ways [86]. Data propose that circRNAs and RBPs cooperate in tumorigenesis. Furthermore, circ-Foxo3 may suppress the cell cycle progress by forming a ternary complex with CDK2 and p21 proteins (the cell cycle proteins) [87]. CDK2 protein is associated with different cancers, including CRC [88], breast cancer [89], and non-small cell lung cancer (NSCLC)[90], therefore, these proteins can be inhibited by the circ-Foxo3 ternary complex. It was demonstrated that some circRNAs in HeLa cells bind HuR. One of them is CircPABPN1 [42]. These results demonstrated that some circRNAs may participate in tumorigenesis by binding to certain proteins.

5. Biomarker potential of circRNAs

A review of ncRNA expression patterns among diverse cancer varieties has proposed that the deregulation of these RNAs expression possibly displays a greater specificity to cancer type and stage compared to alterations in the expression of mRNAs [91]. These worthy discoveries have provided preliminary suggestions that ncRNAs may characterize an unknown pool of diagnostic and therapeutic markers in cancer [16,92]. Therefore, ncRNAs are a major area of interest within the field of tumor biology. The expression pattern of certain circRNAs is frequently cell- and also disease-specific. Therefore, circRNAs represent advantages as biomarkers in different cancer [93]. These molecules are stable and measurable in most bio-fluids, including saliva and blood, which is vital for cancer diagnosis as non-invasive biomarkers [67]. Emerging evidence has revealed a relationship between the expression level of circRNAs and cancer progress, thus researchers increasingly established the diagnostic significance of distinct circRNAs in cancers by comparing them within healthy individuals and cancer cases. For example, in the plasma samples of HCC patients, has_circ_0001445 is significantly down-regulated compared with cirrhosis and hepatitis B patients as well as in healthy individuals [36]. Further analysis indicated that could be serve as a precise marker to make a discrepancy between HCC patents and healthy controls, hepatitis B, or cirrhosis patients [94]. CircRNA in saliva may serve as a biomarker of various diseases. In oral squamous cell carcinoma, salivary circRNAs such as Hsa_Circ_0001971 and Hsa_Circ_0001874 can be considered new diagnostic biomarkers. Zhao *et al.* found that the expression profiles of different circRNAs in saliva samples vary between healthy controls and oral squamous cell carcinoma patients [95]. Further analysis confirmed that has_circ_0001874 has a diagnosis value, however, the combined has_circ_0001971 and has_circ_ 0,001,874 showed a significant diagnosis value for cancer [95]. Interestingly, after surgery, the expression level of circRNAs in saliva was considerably decreased [95]. The roles of circRNAs as possible biomarkers for different cancers were prepared in Table 2.

6. EVs-enclosed circRNAs in cancer

6.1. Overview of EVs

EVs are double phospholipid bilayer vesicles produced from most cells via specific biogenetic and secretory pathways [12,96]. In recent years, EVs have been known as bio-container that can facilitate the transfer of bio-molecular material among cells and also their environment, providing an additional cell-to-cell communication mechanism [12,96]. Cells generate EVs constitutively or following response to /activation by oxidative stress, inflammation, hypoxia, ageing, mechanical stress, and cell death [97–99]. The cargo, membrane constituents, and size of EVs are extremely varied, depending on the origin and type of cell as well as cell and environment conditions [12,96]. Even with heterogeneity, EVs can be categorized into three classes, microvesicles (MVs), exosomes, and apoptotic bodies (ABs) based on their biogenesis pathway and size (Fig. 3). Exosomes are the smallest class of EVs that are generated by the endosomal compartments and the development of intracellular multivesicular bodies (MVBs) enclosing intraluminal vesicles (ILVs), fusion of MVBs with the plasma membrane, and finally, exocytosis with a diameter size rang 30–150 nm [12,96]. MVs are shedding EVs that are produced by the blebbing of the plasma membrane with a size of 100–1000 nm [12,96]. ABs, 100–5000 nm EVs in diameter, are generated from cells enduring apoptosis via outward blebbing and breaking up of the plasma membrane [100]. Exosomes are intensively studied in cancer due to their pivotal roles in cancer development and treatment [101]. Exosomes contain many kinds of biomolecules including proteins, signaling molecules, RNAs, DNA strands, and lipids, which are transferred to distantly and/or neighboring located target cells and act as mediators of intercellular communication, and thus control physiological and pathological states in target cells [102,103]. Exosomes are abundantly present in many bio-fluids and can reach target cells resident distant [104,105]. These EVs generated by tumor cells contain numerous kinds of biomolecules like RNAs ranging from coding and ncRNAs such as mRNAs, miRNAs, lncRNAs, and circRNA that deliver them into target cells and participate in tumorigenesis [106]. Three route have been suggested to distribute cargo of tumor EVs to target cells such as receptor-ligand interaction, endocytosis, and direct fusion with the plasma membrane of target cells [107,108]. Several ways of endocytosis including phagocytosis,

Table 2
CircRNAs as tumor biomarkers in body fluids.

Cancer	CircRNA	Sample	Expression level	Ref
Gastric cancer	Circ-002059 & Circ-0003159	Serum	Down-regulated	[167168169170171172172173174175]
	Circ-0000190	Serum	Down-regulated	
	Circ-0000745	Plasma	Down-regulated	
	Circ-0000663	Plasma	Down-regulated	
	Circ-0000181	Serum	Down-regulated	
	Circ-0000520	Plasma	Down-regulated	
	Circ-0006848	Plasma	Down-regulated	
	Circ-0061276 & Circ-0001017	Plasma	Down-regulated	
	Circ-0001649	serum	Down-regulated	
	hsa_circ_0000673	Plasma	Up-regulated	
Lung cancer	irc-FARSA	Plasma	Up-regulated	[176]
Hepatocellular carcinoma	Circ-0001445	Plasma	Down-regulated	[177127178]
	Circ-104075	Serum	Up-regulated	
		plasma	Down-regulated	
Breast cancer	Circ-0001785 & Circ-0108942	Serum	Up-regulated	[179180]
	Circ-Foxo3	Serum	Down-regulated	
bladder cancer	hsa_circ_0000285	Plasma	Down-regulated	[181]
Esophageal cancer	Circ-TTC17	Plasma	Up-regulated	[182]
Pancreatic cancer	Circ-LDLRAD3	Plasma	Up-regulated	[183184184]
	chr14:101402109–101464448	Plasma	Up-regulated	
	chr14:52729603–52780244	Plasma	Up-regulated	
Nasopharyngeal carcinoma	circRNA_0000285	Serum	Up-regulated	[182]
Oral squamous cell carcinoma	Circ-0001874 &Circ-circ_0001971	Saliva	Up-regulated	[95]
Colorectal cancer	CircMBOAT2	serum	Up-regulated	[185]

receptor-mediate endocytosis, and pinocytosis are implicated in EVs delivery. By receptor-ligand interaction, receptor/ligands located on the surface of EVs interact with molecules located on the target cell membrane. It was demonstrated that EVs derived from neutrophils infected with mycobacterium tuberculosis bear TLR2/6 ligands on their surface [109]. Direct fusion exhibits a feature that EVs membrane fuse with the membrane of target cell and cargo is released into the cytoplasm.

The underlying mechanisms that regulate the sorting of certain circRNAs into exosomes are poorly known. However, three mechanisms may participate in sorting circRNAs into exosomes, including (i) lncRNA may competitively contribute to the loading circRNAs into exosomes. In this regard, the knockdown of lncRNA UCA1 in serum-derived exosomes caused an inhibition in the MAPK signaling and increased the level of circHIPK3 [110]. (ii) Regulation of miRNAs. For instance, when miR-7 was overexpressed in liver tumor cells, the expression of exosomal circCDR1as decreased, whereas the expression level of circCDR1as up-regulated in cells [111]. However, it is uncertain whether the packing of other circRNAs is mediated by changed levels of their related miRs or not. (iii) RBPs based sorting of exosomes circRNAs [110]. In this regard, RBPs may bind specific sequences of circRNAs and direct them into exosomes. For example, exosomes containing RBPs are released from DKs-8 cells. These RBPs can bind circFAT1 and sort circRNAs into exosomes [112].

6.2. Exosomal circRNAs and cancer

Tumor-derived exosomes have been known as key mediators for cancer progression (Fig. 3). Li and co-workers, for the first time, reported that exosomes contain circRNAs [111]. By RNA sequencing analysis, they identified circRNA molecules in MHCC-LM3 liver tumor cells and their exosomes. Compared to parental cells, exosomal circRNAs were resolute at least 2-fold in exosomes. We previously have discussed that exosomes are the metastatic organotropism drivers and can serve as a biomarker for different cancer. Through this review and in this section, we have especially described the fundamental role of exosomes containing circRNAs in cancer development and diagnosis as a biomarker.

6.3. Exosomal circRNAs and metastasis

Metastasis, the migration of cancer cells from primary sites to secondary sites, is a highly regulated and multistep process with an essential role in cancer progression. Exosomal circPTGR1 is up-regulated in HCC and induces metastasis through the miR449a-MET axis [113]. Similarly, in HCC, arsenite-transformed cells release exosomes containing abundantly circRNA_100284 that can induce cell proliferation and the cell cycle progress through miR-217 regulation of EZH2, promoting metastasis [114]. Zong *et al.* showed that up-regulated exosomal circWHSC1 supports ovarian cancer metastasis by sponging miR-1182 and miR-145 and therefore through modulating MUC1 and hTERT [115]. In cholangiocarcinoma, expression of exosomal circ-0000284 was increased, which is associated with the aggressive phenotype of tumor cells and increased metastasis [116]. Circ-IARS of exosomes from pancreatic cancer cells can promote endothelial monolayer permeability by removing miR-122 and subsequently inducing RhoA activity, which participates in tumor cells invasion [117]. Thus, exosomal circRNAs participate in cancer metastasis (Fig. 3).

6.4. Exosomal circRNAs and EMT

EMT is a highly regulated process that initiates the acquisition of mesenchymal phenotype by epithelial cells, meanwhile, remodeling the tumor microenvironment. This process is vital for tumor invasion and metastasis. Chen *et al.* reported that exosomal circPRMT5 promoted bladder cancer via sponging miR-30c. They showed that circPRMT5/miR-30c axis mediated increasing SNAIL1 expression and decreasing E-cadherin expression, which promoted EMT in tumor cells and induced tumor metastasis [118] (Fig. 3). It was revealed that exosomal circNRIP1 may sponge miR-149-5p, regulating the AKT1/mTOR pathway that induced EMT and modified tumor homeostasis, and finally stimulated tumor metastasis [119]. These preliminary studies revealed that exosomal circRNAs can facilitate tumorigenesis by inducing EMT.

6.5. Exosomal circRNAs and angiogenesis

Angiogenesis refers to a process that which new vessels arise from pre-existing vascular [120], the main factor regulating cancer development and metastasis. Exosomal circRNAs are capable of inducing angiogenesis and the permeability of vascular beds. Exosomal circRNA-100338 has been shown to cooperate with NOVA2, which results in permeability in endothelial cells and angiogenesis thus inducing liver tumor cells migration and metastasis [121] (Fig. 3). Knockdown of exosomal circRNA-100338 dramatically suppressed tumor progression and decreased lung metastatic *in vivo* model [121]. Furthermore, exosome-enclosed circSHKBP1 supports the angiogenesis, growth, and invasion of GC cells by modulating the miR-582-3p/HUR/VEGF pathway [122]. As we know, VEGF is one of the vital mediators that stimulate endothelial cells growth.

6.6. Exosomal circRNAs and drug resistance

Drug resistance is the main challenge in the treatment of cancers. Exosomal circRNAs can induce drug resistance. For instance, Zhang and co-workers reported that exosomal circUHRF1 from tumor cells induced NK cells enervation and might promote resistance to anti-PD1 treatment in HCC cells [121] (Fig. 3). Temozolomide, a chemotherapy drug, is frequently utilized for the therapy of glioma [123]. Exosomal circNFIX induced Temozolomide resistance in glioma and promoted tumor development [124]. Authors reported that inhibition of circNFIX boosted the sensitivity of glioma cells to Temozolomide where certain pathways are implicated in the exosomal circNFIX and miR-132 interaction [124] (Fig. 3). This result may provide us with an understanding of the drug-resistant mechanism in glioma cells for targeting exosomal circNFIX to overcome drug resistance. In the same way, in glioma cells, exosomal circHIPK3 has been shown to promote the development and resistance against Temozolomide by modulating the miR-421/ZIC5 pathway [125]. These results show that exosomal circRNAs can participate in drug resistance and they may be new targets for cancer–resistance therapies.

6.7. Biomarkers potential of exosomal circRNAs

As mentioned, EVs are distributed through several body fluids, therefore they can be available in a simple liquid-biopsy and non-invasive way. According to studies, exosomes can serve as a fingerprint of tumor cells as they contain the same biomolecules as tumor cells express [7,126]. In addition, it was shown that divergence in the expression level of certain circRNAs in exosomes isolated from the body fluids was correlated to the pathological condition of tumor stage. For example, It was revealed that exosomal has_circ_0002577 and has_circ_0109046 were up-regulated in the serum samples of patients with endometrial cancer [127], representing their potential function as biomarkers for endometrial cancer. In another study, Wu *et al.* showed that exosomal circFNDC3B was increased in the sera samples of patients with papillary thyroid cancer compared with healthy individuals, suggesting a new diagnostic biomarker for this cancer [128]. We prepared Table 3 representing the possible role of exosomal circRNAs as tumor biomarkers.

7. CircRNAs as a novel target for cancer therapy

Recent development in circRNAs study has discovered fundamental

Table 3
Biomarker potential of exosomal circRNA in cancer.

Cancer	Exosomal circRNA	Biofluid	Expression level	Application	Ref
Bladder cancer	Circ-0109046 & Circ-0002577	Serum	Up-regulated	Early diagnosis	[186]
Hepatocellular Carcinoma	Circ-PTGR1	Serum	Up-regulated	Diagnosis	[113187188]
	Circ–100338	Serum	Up-regulated	Prognosis	
	Circ-0006602	Serum	Up-regulated	Early diagnosis	
Pancreatic Cancer	Circ-PDE8A	Serum	Up-regulated	Diagnosis or progression.	[189117]
	Circ-IARS	serum	Up-regulated	Diagnosis and prognosis	
Lung Cancer	Circ-0056616	Serum	Up-regulated	Detection of lymph node metastasis	[190]
Gastric Cancer	Circ-0000419 Circ-RanGAP1	Serum	Up-regulated	Diagnostic/prognostic biomarker	[191192193]
	Circ-KIAA1244	Serum	Down-regulated	Diagnostic/prognostic biomarker	
		Serum	Down-regulated	Prognostic biomarker	
Bladder Urothelial Carcinoma	Circ-PRMT5	Urine	Up-regulated	Early diagnosis	[118]
Laryngeal Squamous Cell Carcinoma	Circ-RASSF2	serum	Up-regulated	Preoperative diagnosis	[194]
Colorectal cancer	Circ-0004771	Serum	Up-regulated	Diagnostic biomarker	[195]
Papillary Thyroid Cancer	Circ-FNDC3B	Serum	Up-regulated	Early diagnosis and prognosis	[128]

features of circRNA biogenesis and function, however, we are still required to study further the mechanism involved in circRNAs expression and their roles of them in normal cells/tissues and diseased cells/tissues. We know that circRNAs contribute to tumorigenesis through different mechanisms. Thousands of circRNAs are expressed in various tissues with different roles and properties. To date, there have been no preclinical and clinical studies targeting circRNAs for cancer treatment as well as using them as therapeutic vectors but it seems that this trend will alter in the future. The exceptional stability and ability to remove (sponge) various miRs and proteins could make circRNAs a hopeful approach for the transfer of therapeutic agents. Having several binding positions for various miRs and proteins, may renovate controlled growth of the tumor cells or promote cell death. Furthermore, Pol II promoters are a pattern for the formation of circRNAs, therefore, this feature raises the idea that they may be targeted in a cell-specific manner using certain promoters or by specific tumor-activated regulatory elements. Using circRNAs as therapeutic targets may face challenges that should be considered. Targeting certain circRNAs must be correctly done so that does not affect the expression of mRNA. In this context, a practical method should be designed to target the only back-splice junction of

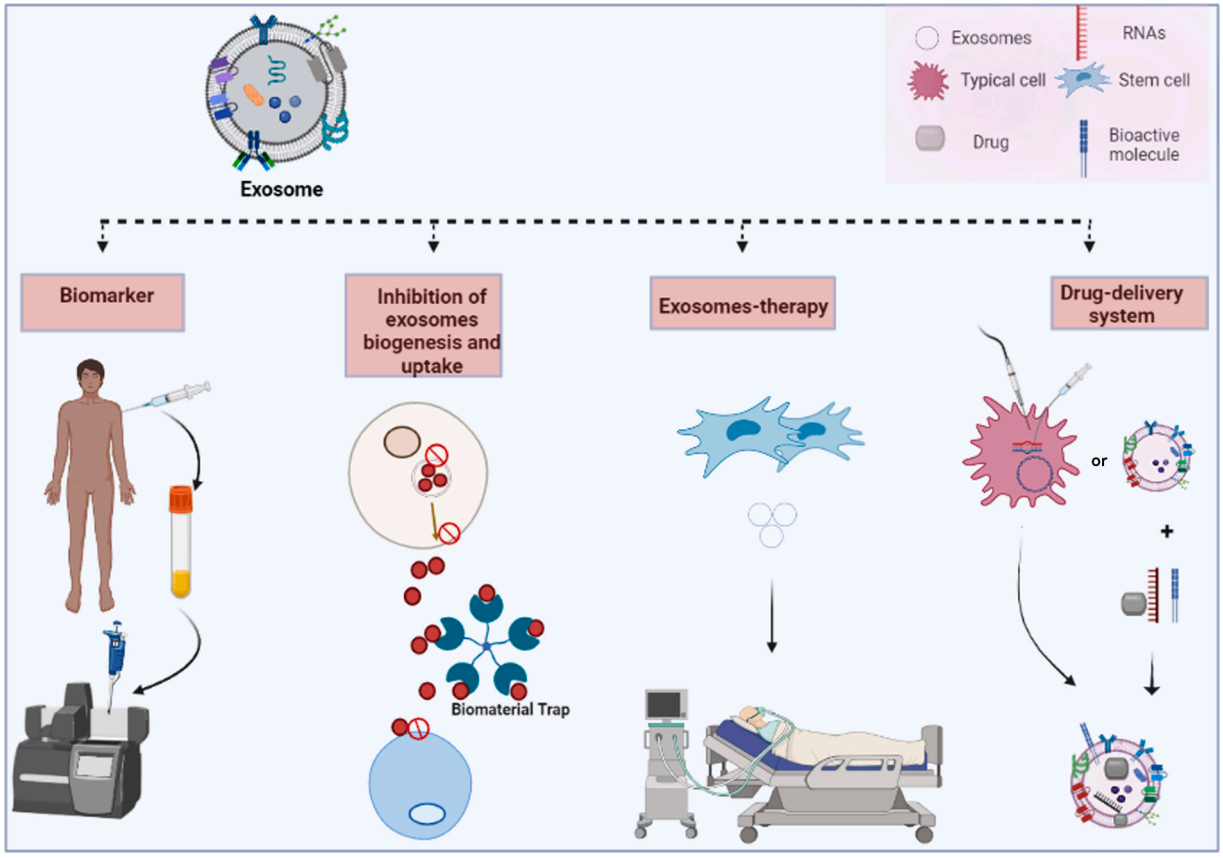

Fig. 4. Application of exosomes in cancer management. Cancer-derived exosomes containing circRNAs are useful tool for the diagnosis and prognosis of different cancer as novel biomarker. In addition, inhibition of exosomes biogenesis and uptake may be a possible application of exosomes containing circRNAs for suppressing cancer. Exosomes derived from certain and safe source cells can be used for the treatment of cancer, which is known as exosomes-therapy. Exosomes can be loaded with therapeutic reagents and known as a drug-delivery system that transfer reagents to inhibit/degrade oncogenic circRNAs in tumor cells. Besides, cells may be genetically engineered to produce certain optional exosomes enriched with anti-cancer circRNAs.

target circRNAs via exogenously delivering siRNA entirely complementary to this location. Instead, proper antisense oligonucleotides, which target distinct locations like binding sites of RBPs and flanking intronic Alu repeats may be useful for inhibiting the back-splicing process in the pre-mRNA. To up-regulate the expression of tumor-suppressor circRNAs, gene therapy using DNA cassettes planned for circRNAs expression can be useful. A possible way is to clone the relative exons and splice sites circRNAs to increase the expression of circRNAs. Another possible application of circRNAs in cancer is the use of exosomes containing circRNAs (Fig. 4). For example, inhibition of exosomes biogenesis from cancer cells may be a new strategy to overcome cancer metastasis as these exosomes are enriched with oncogenic circRNAs [129]. This idea may face challenges because we do not know how and which drugs/inhibitors can preferentially inhibit exosomes from tumor cells, therefore needs further studies [129]. Furthermore, these exosomes can be trapped by an artificial biomaterial implanted in tumor location, however, selecting a biocompatible and being invasive method are concerns associated with this idea (Fig. 4). We think that exosome-therapy may serve as another application where exosomes encompassing anti-cancer circRNAs are used. In this regard, exosomes from safe and confident source cells can be isolated and administrated to the tumor in proper ways. In addition, exosomes may be modified to release artificial exosomes with specific tumor suppressor circRNAs [130,131]. Exosomes can be loaded with therapeutic reagents and called a drug-delivery system that delivers reagents to inhibit/degrade oncogenic circRNAs in tumor cells (Fig. 4). Moreover, certain cells can be genetically engineered to generate specific exosomes containing anti-cancer circRNAs. It seems that side and non-targeting effects are associated with these exosomes. Further studies are intensively desirable to approve the possibility and validity of these methods and the clinical translation of circRNAs in cancer management.

8. Conclusion and future perspectives

Recent advancement in the circRNA field has revealed the biogenesis mechanisms and pivotal roles of these molecules in cancer progression. The investigation of circRNAs in cancer is yet in its initial stages, and detailed information and the underlying mechanism are lacking. Thousands of types of circRNAs in various tissues and diseases have been recognized with limited functionally studied. In cancer, circRNAs can participate in tumorigenesis by different mechanisms. Therefore, the accumulation of the circRNAs in cells/tissues may be good or bad based on the nature/function of circRNAs. In cancer, for example, some circRNAs are anticancer and can sponge onco-miRs and onco-proteins, therefore these circRNAs are useful and good for the treatment of cancer.. Emerging evidence shows that exosomes derived from tumor cells contain various circRNAs. These circRNAs when reach target cells participate in regulating several signaling pathways, participating in cancer development. Now, we know that exosomal circRNAs regulate tumor cells proliferation, invasion, EMT, metastasis, angiogenesis, and drug resistance. Exosome of tumor cells may represent a double-edged sword for circRNAs. In this context, two assumptions of circRNAs in exosomes have been suggested; (i) exosomes protect circRNAs from degradation and clearance and transfer them into target cells, participating in cell-to-cell communication, and (ii) exosome may participate in reducing circRNAs accumulation inside a cell and help circRNAs clearance. A study showed that cells may remove circRNA by expelling them via exosomes that may be uptaken by other cells like macrophages [132]. Which circRNAs should be transferred or removed from a cell, and how distinct circRNAs are loaded within exosomes, are the key questions in the field and need further investigation. Cell condition and type may be implicated in these questions. We do not exactly know circRNAs are sorted into exosomes actively or/and passively, and how exosomal circRNAs are eventually degraded. Although circRNAs are resistant to exonucleolytic degradation, they possibly have endonuclease sites that make them degradable by specific enzymes. Therefore, under different conditions, the mechanisms behind the biogenesis and degradation of exosomal circRNAs need further investigation. Another question is whether the function of tumor exosomes is only related to their circRNA cargo? We think this is a controversial at last of two facts, first; other bioactive molecules in exosomes may affect the analysis of exosomal circRNAs findings. Second, various isolation and characterization techniques cause discrepancies in the results of analysis [133]. Thus, more advanced and efficient techniques are in critical requirement. As abovementioned, exosomal circRNAs may open a new avenue for the treatment of cancer and clinical applications. First, exosomal circRNAs are likely a worthy applicant for the diagnosis of cancer as a biomarker. Exosomes are present in most body fluids, therefore by a simple liquid biopsy exosomal circRNAs are accessible to analysis. The expression of pattern of circRNAs can be useful for prognostic and diagnostic biomarker studies. This bears limitations, such as exosomes contain low levels of circRNAs, therefore they are challenging to be distinguished in exosomes by a precise method and algorithms. In addition, the sequence overlap and circular conformation with linear mRNA equals have made the accurate assessment of circRNAs expression challenging. Second, exosomes can serve as a drug-delivery system [134]. In this vision, exosomal delivery of circRNAs may exhibit therapeutic benefits. As we know, the key function of circRNAs is their roles as proteins and miRNA sponges. CircRNAs have a specific structure and stability that can effectively regulate miRNAs and proteins in target cells/tissues, inhibiting cancer. In the near future, researchers should determine which circRNAs are suitable for incorporating into exosomes to inhibit tumor cells effectively. In addition, the source of exosomes and proper loading methods need to be precisely discovered. Third, some non-cancerous cells may produce exosomes with anticancer circRNAs, which could be useful for the treatment of cancer. This approach requires additional scrutiny. Fourth, previous studies have suggested that removing tumor exosomes or/and inhibiting their biogenesis may contribute to reducing tumorigenesis [135]. However, side effects and unwanted results could be associated with this approach. Overall, this section shows the clinical significance of exosomal circRNAs, however, there exists inadequate evidence for circRNAs clinical application and there are many concerns regarding the application and clinical translational of exosomal circRNAs that should be considered in further investigations.

CRediT authorship contribution statement

Ali Vahabi: Conceptualization, Data curation. **Jafar Rezaie:** Conceptualization, Data curation, Supervision, Writing - review & editing. **Mehdi Hassanpour:** Investigation, Methodology. **Yunes Panahi:** Investigation, Methodology. **Mohadeseh Nemati:** Software. **Yousef Rasmi:** Visualization, Writing - original draft. **Mahdieh Nemati:** Visualization, Writing - original draft.

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