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Review

The Function, Underlying Mechanism and Clinical Potential of Exosomes in Colorectal Cancer

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Abstract

Colorectal cancer (CRC) is a lethal malignancy worldwide. Exosomes are extracellular vesicles derived from the endosomal pathway of nearly all cells and can be found in body fluids. They can be considered an intercellular system in the human body that can mediate near- and long-distance intercellular communication due to their features and functions. Investigations have revealed that exosomes are participated in different processes, physiologically and pathologically, especially in cancer. However, the clinical value of exosomes and their mechanisms of action in CRC are unclear and have not been systematically assessed. The purpose of this review is to discuss how exosomes play a role in the occurrence and development of CRC, with a particular focus on the functions and underlying mechanisms of tumor-derived exosomes as well as non-tumor-derived exosomes. We also describe the evidence that exosomes can be used as diagnostic and prognostic markers for CRC. In addition, the possibilities of exosomes in CRC clinical transformation are also discussed.

Keywords: colorectal cancer; exosome; biomarker; diagnosis; clinical transformation

1. Introduction

Worldwide, colorectal cancer (CRC) is a common malignant tumor [1]. According to the Global Cancer Statistics 2020, CRC is the third most commonly diagnosed cancer, the second leading cause of cancer death in women, and the third leading cause of incidence and mortality in men [2]. It is a malignancy originating from the mucosal epithelium and glands of the large intestine. Histologically, there are several subtypes of CRC, and approximately 90% of CRCs are adenocarcinomas [3]. Patients with CRC often present with anemia, blood in the stools, aberrant bowel movement, and weight loss [4]. It has been demonstrated that the occurrence of CRC is related to dietary patterns, metabolism, and inflammation [5]. The initiation and progression of CRC may also be affected by environmental and genetic factors [6]. Thus, CRC is the result of a complex multi-step process involving numerous factors and genes. For patients with CRC, the systemic treatment regimens utilized for clinical management include tumor resection, 5-Fluorouracil-based chemotherapy, radiotherapy, anti-angiogenic treatment, targeted therapy, and immunotherapy [7–9]. Although the death rate of CRC has decreased due to earlier screenings and improved treatments, more than one-third of patients die within 5 years of initial diagnosis, with liver metastases being the most fatal cause of death [10–12].

Exosomes are extracellular vesicles (EVs) with diameters ranging from 40 to 160 nm. They are derived from the endosomal pathway of nearly all cells, and they can be found in cell culture fluids, breast milk, blood, urine, pleural effusion, saliva, and other body fluids [13–15]. Exosomes carry specific cargo consisting of DNA, RNA, cytosolic and cell-surface proteins, metabolites, and lipids. They can be thought of as an intercellular system in the human body that mediate communication between cells and influence a variety of cell biological behaviors [13,16]. During the generation of exosomes, the plasma membrane is double invaginated, and intracellular multivesicular bodies (MVBs) containing intraluminal vesicles (ILVs) are formed. MVBs fuse to the plasma membrane, and ILVs are ultimately secreted as exosomes through exocytosis. The uptake of exosomes is not random but depends on the surface proteins on the membrane of exosomes and recipient cells [17]. When exosomes encounter suitable recipient cells, exosomes can adhere to the surface of recipient cells through the interaction of ligands and receptors. They can directly fuse with cell membranes or be endocytosed by recipient cells and release the cargo into target cells (Fig. 1) [13,14]. Numerous studies have shown that exosomes are involved in different physiological and pathological processes, such as inflammatory responses, cancer development, metastasis, and immunity [17,18].

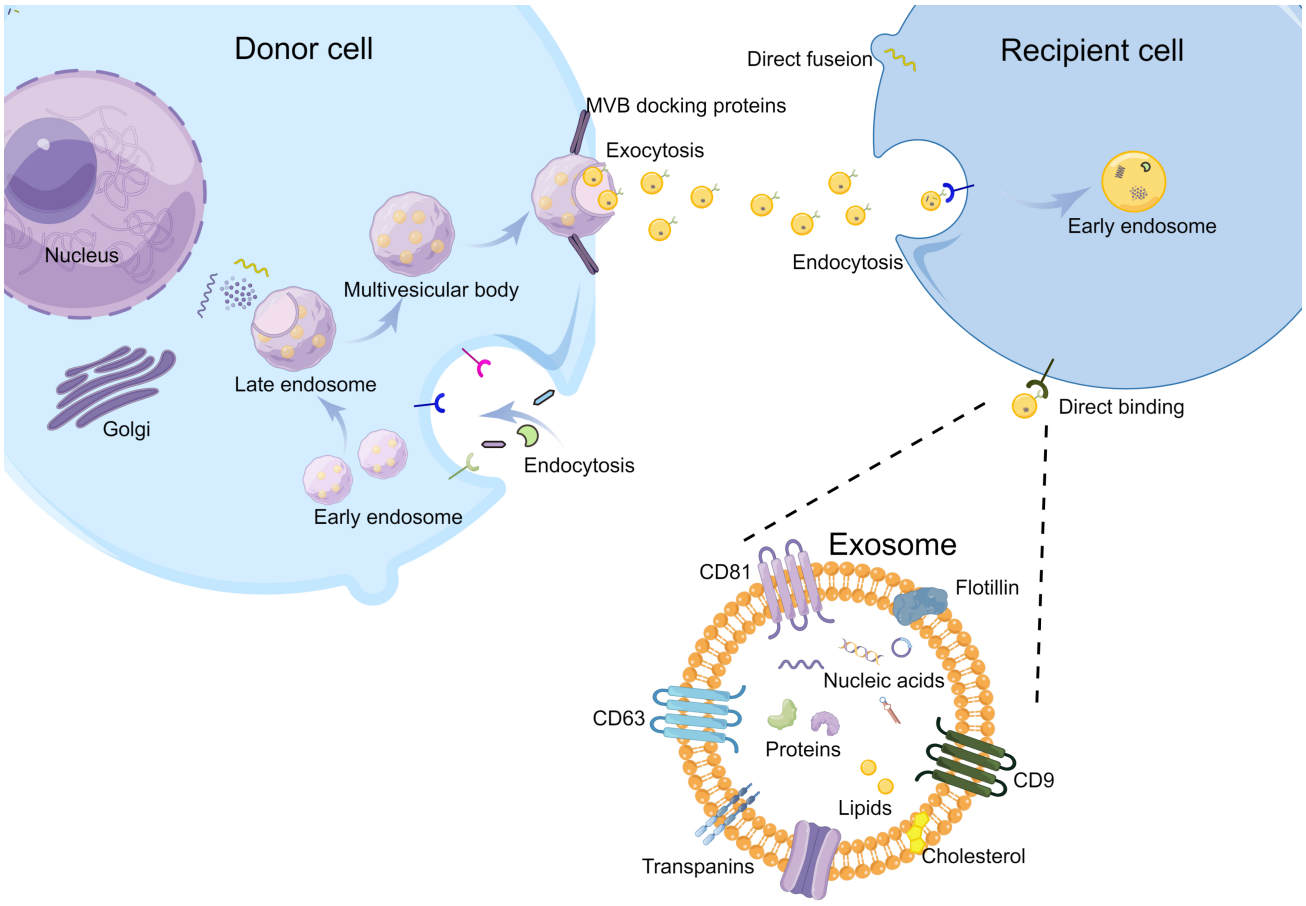

Fig. 1. Biogenesis and intercellular communications of exosomes. The plasma membrane is double invaginated, forming the intracellular multivesicular bodies (MVBs) containing intraluminal vesicles (ILVs). MVBs fuse to the plasma membrane, and ILVs are ultimately secreted as exosomes through exocytosis. The intercellular communications of exosomes depend on the interactions between ligands and receptors. When the exosomes meet the proper recipient cells, they can directly fuse with cell membranes or be endocytosed by recipient cells and release the cargo into target cells.

Recently, it has been demonstrated that exosomes play a role in the occurrence, development, invasion, metastasis, tumor microenvironment (TME) remodeling, chemoresistance, and other processes in CRC [19]. This paper reviews the functions and underlying mechanisms of action of tumor-derived and non-tumor-derived exosomes in CRC, intending to summarize the previous studies on potential biomarkers and effective targets for the treatment of CRC.

2. Physiological and Pathological Functions of Exosomes

Exosomes were first reported as a "type of small vesicles" in 1983, and the name "exosome" was first used in 1989 [20,21]. They were initially believed to be superfluous membrane vesicles during cell maturation, with the effect of regulating membrane function, removing cellular debris, and eliminating surface molecules [14]. However, exosomes have successfully attracted attention among researchers because of their special roles in multiple facets of cell activity.

Exosomes can be secreted by the donor cells through exocytosis and accepted by the recipient cells through endocytosis or directly fusing to cell membranes. Thus, exosomes act as a medium in intercellular communications and transmit information to a large number of cells and locations, physiologically or pathologically (Fig. 2).

Exosomes are involved in the signal transduction of the nervous system due to reciprocal signal transfer among sensory and motor neurons, interneurons, and glial cells [22]. Moreover, they play an important role in the aging process [23]. Exosomes also play an important role in reproductive development. They are involved in gamete maturation, fertilization, embryo implantation, immunological communication between the mother and the fetus, and fetal protection by regulating local and/or systemic immune responses, organ development, and melanin synthesis [24–28]. Additionally, exosomes are related to cell proliferation, homeostasis, and maturation, such as in hepatocytes and reticulocytes [20,29].

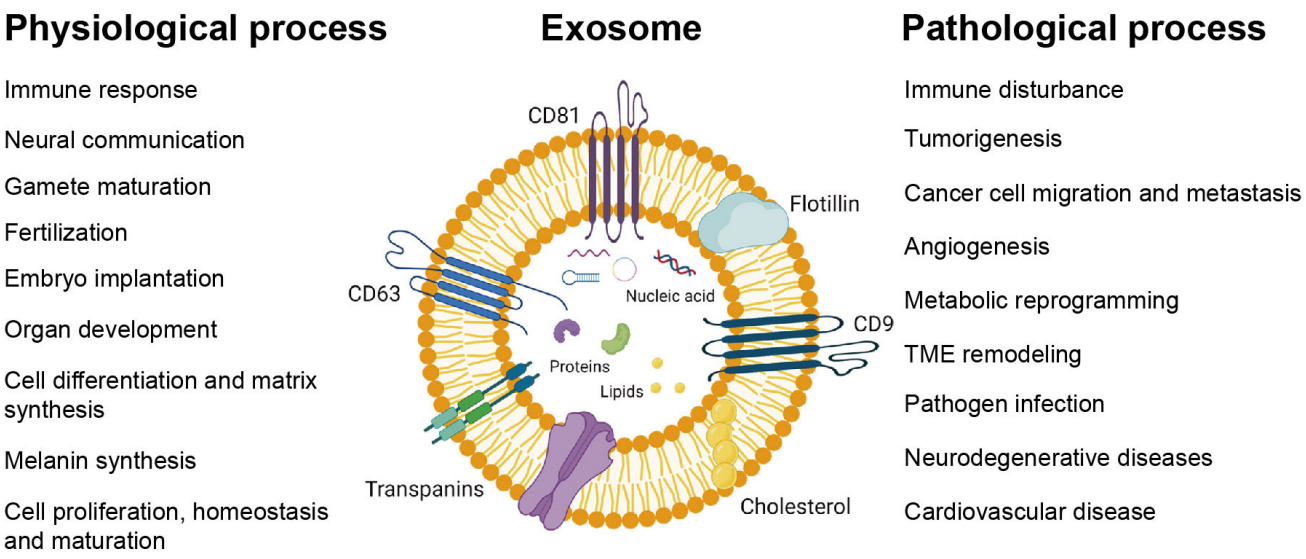

Fig. 2. Exosomes play a role in physiological and pathological processes. Exosomes are involved in basic physiological processes such as immune response, neural communication, gamete maturation, fertilization, embryo implantation, organ development, cell differentiation and matrix synthesis, melanin synthesis, cell proliferation, homeostasis, and maturation. They are also involved in some pathological processes, such as immune disturbance, tumorigenesis, cancer cell migration and metastasis, angiogenesis, metabolic reprogramming, tumor microenvironment (TME) formation, pathogen infection, neurodegenerative diseases, and cardiovascular disease.

Exosomes are involved in immune response and infection [30,31]. They participate in antigen presentation and induce the activation of T and/or B cells [32]. The contents of exosomes are involved in regulating innate and adaptive immune responses. It has been demonstrated that the DNA of some intracellular bacteria sorted into exosomes is able to activate innate immune responses or lower antibacterial defenses [33].

Numerous studies have demonstrated that exosomes are widely involved in the occurrence and development of cancers. They are a double-edged sword in tumor growth and progression. For example, exosomes derived from M2 macrophages can inhibit the migration and invasion of glioma cells [34]. Alternatively, the impact of tumor exosomal DNA on inflammatory responses can indirectly worsen cancer [35]. In addition, tumor-derived exosomes can promote immune evasion by cancer cells and generate an immunosuppressive microenvironment [17,36]. Exosomes derived from tumor cells may be absorbed by surrounding cells and transform the microenvironment into one that is prone to tumor development [37]. They also participate in tumor growth, metastasis, apoptosis, metabolic reprogramming, extracellular matrix degradation, stromal reprogramming, immune surveillance escape, and drug resistance [23,38,39]. In addition, exosomes are involved in neurodegenerative diseases, cardiovascular disease, and pathogenic infections [14,40].

3. The Underlying Mechanisms of Exosome Functions in CRC

Numerous studies have explored the relationship between exosomes and the pathogenesis of different cancers. The data demonstrated that exosomes have a relationship with the hallmarks of cancer, such as sustaining proliferation signaling, activating invasion and metastasis, inducing angiogenesis, metabolic reprogramming, and immune evasion [41]. We reviewed the functions and mechanisms of exosomes in CRC, including CRC cell-generated exosomes and non-tumor cell-produced exosomes.

3.1 CRC Tumor-Derived Exosomes

Tumor-derived exosomes (TDEs) were first named in 1981, and it has attracted much attention in the past years [42]. Exosomes act as signal messengers or transducers for communications between cells [43]. Once the recipient cells take up TDEs, the exosomes are internalized, and exosomal contents (such as microRNA, lncRNA, and circRNA) are released. The recipient cells respond to these exosomal contents by changing their phenotypes. This process is finely regulated and specifically determined by complex surface molecules on the extracellular vesicles and the recipient cell membrane [44]. This paper will summarize the functions and mechanisms of tumor-derived exosomes in CRC (Fig. 3; Table 1, Ref. [45–92]).

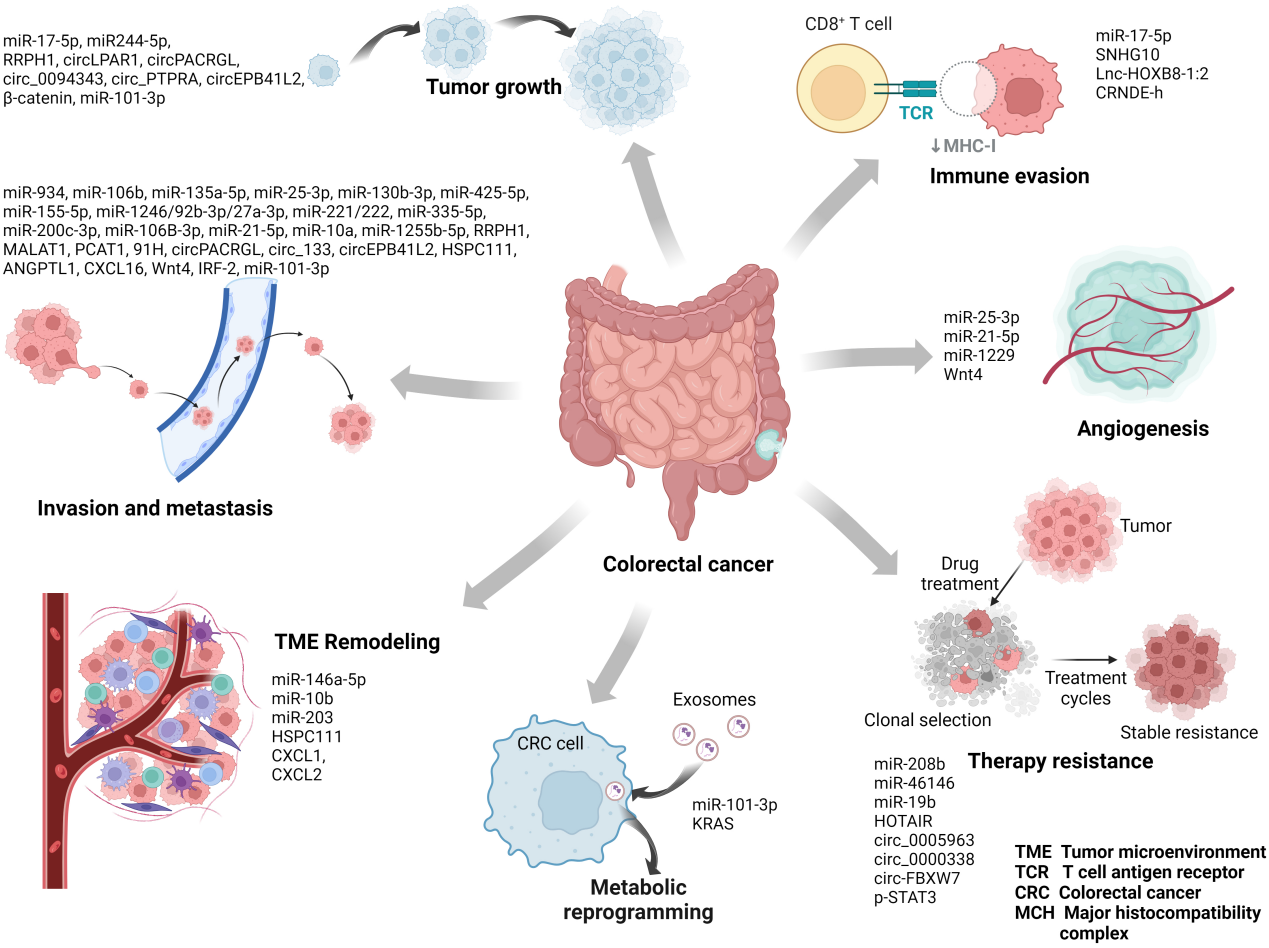

Fig. 3. Mechanism of tumor-derived exosomes in colorectal cancer (CRC). Exosomes derived from CRC cells can transport their cargo to other cells and play an important role in the occurrence and progression of CRC, including tumor growth, invasion and metastasis, angiogenesis, immune evasion, TME remodeling, metabolic reprogramming, and therapy resistance.

3.1.1 Tumor Growth

One of the typical hallmarks of cancer is sustaining proliferation signaling, ultimately causing the rapid growth of the tumor. CRC tumor-derived exosomes (CTDEs) can regulate the growth of CRC cells through a variety of pathways, such as involvement in cell proliferation, cell cycle, and apoptosis. For example, *circLPAR1* is encapsulated by CRC cell exosomes, internalized by CRC cells, and inhibits tumor growth. The investigation of underlying mechanisms showed that exosome *circLPAR1* might bind to *eIF3h* directly and inhibit *METTL3-eIF3h* interaction, ultimately reducing the translation of *BRD4* [45]. Exosome-carried *circ_0094343* derived from CRC cells plays an inhibitory role in the proliferation and clone formation of HCT116 cells via the *miR-766-5p/TRIM67* axis [46]. Exosomal *circ_PTPRA* can function as a competing endogenous RNA (ceRNA) and increase the expression of *SMAD4* by binding to *miR-671-5p*, ultimately inducing CRC cell cycle arrest and inhibiting cell proliferation [47]. It has also been demonstrated that a hypoxic microenvironment in CRC may promote tumor cells to release exosomes rich in *miR-410-3p*. These exosomes may transfer to normoxic cells and enhance the proliferation of normoxic CRC cells [93]. Exosomal *circEPB41L2* derived from CRC cells could suppress CRC cell proliferation and promote apoptosis by serving as a sponge for *miR-21-5p* and *miR-942-5p* and regulating the *PTEN/AKT* signaling pathway [48]. CRC cell exosome *miR-224-5p* promotes cell proliferation by downregulating *CMTM4*, thus promoting the malignant transformation of human normal colonic epithelial cells [49]. Oncogenic mutant *β-catenin* contained in the extracellular vesicles can activate the *Wnt* signaling pathway in the recipient cells and increase tumor burden *in vivo* [50].

3.1.2 Invasion and Metastasis

Invasion and metastasis are the leading causes of cancer-associated death in patients with CRC; however, the molecular mechanisms underlying tumor invasion and metastasis are complex and elusive [94]. Numerous studies

Table 1. The function and mechanism of tumor-derived exosomes in CRC.

Type	Molecule	Function	Target	Ref.
miRNA	*miR-934*	Promote colorectal cancer liver metastasis	*PTEN*	[51]
	miR-106b	Promote migration, invasion, and metastasis	*PDCD4*	[53]
	miR-135a-5p	Promote CRC liver metastasis	*kinase 2-yes-associated protein-MMP7 axis*	[54]
	miR-25-3p	Facilitate vascular permeability and angiogenesis	*KLF2, KLF4*	[68]
	miR-25-3p, miR-130b-3p, miR-425-5p	Enhance M2 polarization of macrophages and induce liver metastasis of CRC		[95]
	miR-208b	Treg expansion, oxaliplatin resistance	*PDCD4*	[72]
	miR-146a-5p, miR-155-5p	Activate CAFs and enhance the invasive capacity of CRC cells	*SOCS1, ZBTB2*	[78]
	miR-1246/92b-3p/27a-3p	Promote metastasis		[57]
	miR-21-5p	Induce angiogenesis and vascular permeability	*KRIT1*	[69]
	miR-221/222	Promote metastasis	*SPINT1*	[58]
	miRNA-335-5p	Promote migration, invasion, and metastasis	*RASA1*	[59]
	miR-200c-3p	Inhibit migration and invasion, and promote apoptosis after LPS stimulation	*ZEB-1*	[60]
	miR-46146	OX resistance	*PDCD10*	[89]
	miR-106b-3p	Promote metastasis	*DLC-1*	[61]
	miR-19b	Enhance radioresistance and stemness of CRC cell	*FBXW7*	[90]
	microRNA-21-5p	Induce an inflammatory premetastatic niche	*TLR7*	[63]
	miR-1229	Promote angiogenesis	*HIPK2*	[70]
	miR-17-5p	Promote CRC cell growth and inhibit anti-tumor immunity	*SPOP*	[76]
	miR-10a	Promote lung metastasis		[66]
	miR-10b	Activate fibroblasts to become CAFs	*PIK3CA*	[82]
	miR-1255b-5p	Suppress EMT and liver metastasis	*hTERT*	[67]
	miR-224-5p	Promote tumor growth	*CMTM4*	[49]
	miR-203	Promote the differentiation of monocytes to M2-TAMs		[83]
	miR-101-3p	Be related to metabolic reprogramming, promote tumor growth, migration, and 5-FU resistance	*HIPK3*	[84]
lncRNA	*RPPH1*	Promote metastasis and proliferation	*TUBB3*	[55]
	SNHG10	Contribute to immune escape	*INHBC*	[73]
	lnc-HOXB8-1:2	Lead to TAM infiltration and M2 polarization	*hsa-miR-6825-5p*	[74]
	CRNDE-h	Promote Th17 cell differentiation	*RORγt*	[75]
	MALAT1	Promote the invasion and metastasis	*miR-26a/26b*	[62]
	PCAT1	Promote EMT and liver metastasis	*miR-329-3p*	[65]
	HOTTIP	Increase resistance of CRC cells to mitomycin	*miR-214*	[92]
	91H	Enhance CRC metastasis	*HNRNPK*	[49]
	HOTAIR	Impede anti-tumor immunity	*PKM2*	[77]
circRNA	*CircLPAR1*	Suppress tumor growth	*eIF3h*	[45]
	CircPACRGL	Promote proliferation, invasion, migration, and differentiation of N1 to N2 neutrophils	*miR-142-3p/miR-506-3p*	[52]
	Circ-133	Promote cell migration	*GEF-H1*	[56]
	Circ_0005963	Promote chemoresistance	*miR-122*	[86]
	circ_0000338	Improve the chemoresistance	*miR-217 and miR-485-3p*	[88]
	circ_0094343	Inhibit proliferation, clone formation, and glycolysis	*miR-766-5p*	[46]
	circ_PTPRA	Induce CRC cell cycle arrest and inhibited cell proliferation	*miR-671-5p*	[47]
	circ-FBXW7	Ameliorate chemoresistance to oxaliplatin in CRC	*miR-128-3p*	[91]
	circEPB41L2	Suppress CRC cell proliferation, migration, and invasion and promote apoptosis	*miR-21-5p, miR-942-5p*	[48]

Table 1. Continued.

Type	Molecule	Function	Target	Ref.
Others	*HSPC111*	Altered lipid metabolism of CAFs and promote liver metastasis	*ACLY*	[79]
	p-STAT3	Promote 5-FU resistance		[87]
	ANGPTL1	Attenuate CRC liver metastasis	*MMP9*	[80]
	CXCL16	Promote metastasis		[57]
	Wnt4	Enhance migration and invasion		[64]
	IRF-2	Remodel the lymphatic network and promote metastasis	*VEGFC*	[70]
	CXCL1, CXCL2	Attract CRCSC-primed neutrophils to promote tumorigenesis of CRC cells	*IL-1β*	[81]
	Wnt4	Promote Angiogenesis	*β-Catenin*	[71]
	β-catenin	promote cancer progression	*Wnt signaling pathway*	[50]
	KRAS	Alter the metabolic state of recipient colonic epithelial cells		[85]

have shown that CTDEs are associated with the invasion and metastasis of CRC. For example, tumor-derived exosomes *miR-934* can target *PTEN*, resulting in downregulation of the *PTEN* expression, which in turn activates the *PI3K/AKT* signaling pathway to induce M2 macrophage polarization, ultimately promoting CRC liver metastasis [51]. Cancer-derived exosomal *circPACRGL* can absorb *miR-142-3p/miR-506-3p* as a sponge and facilitate the *TGF-β1* expression, thus promoting CRC cell migration and invasion [52]. The exosomes of CRC cells which have undergone EMT contain *miR-106b*, and *miR-106b* in exosomes can directly inhibit *PDCD4* post-transcriptionally, activate the *PI3Kγ/AKT/mTOR* signaling pathway, and promote the M2 polarization of macrophages. Activated M2 macrophages promote EMT-mediated CRC cell migration, invasion, and metastasis in a positive feedback manner [53]. The hypoxic microenvironment in the CRC primary lesion promotes exosome release, selectively initiating the formation of a favorable premetastatic niche in the liver. Molecular mechanism exploration has found that Kupffer cells (KCs) can engulf exosomes containing *miR-135a-5p*, which enter the liver from the blood circulation. Exosomal *miR-135a-5p* initiates the large tumor suppressor *kinase 2-yes-associated protein-MMP7* axis and promotes CRC liver metastasis [54]. Exosome-encapsulated miRNAs, which are from CRC cells, can enhance the M2 polarization of macrophages and contribute to *CXCL12/CXCR4*-induced liver metastasis of CRC [95]. LncRNA *RPPH1* is significantly upregulated in CRC tissues, and it could be encapsulated in the exosomes of CRC cells. Then, exosomes rich in *RPPH1* are transported into macrophages and mediate macrophage M2 polarization, thereby promoting metastasis and proliferation of CRC cells [55]. Hypoxia can induce the secretion of *circ-133*-rich exosomes, which are transported into normoxic cancer cells. *Circ-133* contained in the exosomes promotes cell migration via the *miR-133a/GEF-H1/RhoA* axis [56]. Exosomal *miR-27b-3p* secreted after epithelial-mesenchymal transformation of CRC cells increases vascular permeability and promotes the production of circulating tumor cells (CTCs), thus promoting the metastasis of CRC [96]. *HuR*, which is an RNA-binding protein contained in CRC-derived exosomes, can stabilize *c-Myc* mRNA and promote lung cell proliferation [97]. *Fusobacterium nucleatum* infection may stimulate tumor cells to generate exosomes rich in *miR-1246/92b-3p/27a-3p* and *CXCL16/RhoA/IL-8* that are delivered to uninfected cells to promote metastatic behaviors in CRC [57]. Exosomal *miR-221/222* targets *SPINT1* and plays a key role in forming a favorable premetastatic niche (PMN), thus leading to the metastasis of CRC [58]. Exosome-transmitted *miRNA-335-5p* derived from metastatic CRC cells promotes CRC migration, invasion, and metastasis which may be due to EMT caused by *RASA1* [59]. *MiR-200c-3p* in exosomes derived from CRC cells influences the exosomal expression of *ZEB-1* mRNA, and further alters *ZEB-1* protein expression in CRC cells, ultimately inhibiting CRC migration and invasion after LPS stimulation [60]. CRC-derived exosomal *miR-106b-3p* promotes metastasis by down-regulating *DLC-1* expression. Serum exosome *miR-106b-3p* could be a potential molecular biomarker for prognosis and may be a target for the treatment of CRC [61]. Exosomal *MALAT1* sponges *miR-26a/26b*, enhances *FUT4* fucosylation, and activates the PI3K/Akt pathway, ultimately promoting the invasion and metastasis of CRC [62]. *MicroRNA-21-5p* is highly enriched in CRC-derived exosomes and is essential for creating a liver proinflammatory phenotype and liver metastasis of CRC by inducing an inflammatory premetastatic niche through the *miR-21-TLR7-IL-6* axis, therefore promoting liver metastasis [63]. Exosomal *miR-193a* and *let-7g* facilitate cancer primary CRC progression and peritoneal metastasis by targeting *MMP16* and *CDKN1A* [98]. It is also demonstrated that hypoxia may promote the release of *Wnt4*-rich exosomes which are derived from tumor cells. The *Wnt4*-rich exosomes are delivered to normoxic cells and facilitate the migration and invasion of normoxic CRC cells [64]. Exosomal *IRF-2*

remodels the lymphatic network in a sentinel lymph node (SLN) and may predict the development of CRC lymph node (LN) metastases [99]. Exosomes rich in *circPABPC1* are transported from CRC cells to CRC cells and are involved in the progression of CRC. In the nucleus, *circPABPC1* initiates the transcription of *HMGA2* by recruiting *KDM4C* to its promoter and reducing the H3K9me3 modification. In the cytoplasm, it inhibits the degradation of *ADAM19* and *BMP4*, which is mediated by *miR-874* and *miR-1292*. Thus, *circPABPC1* facilitates liver metastasis in CRC via upregulating the expression of *HMGA2*, *BMP4*, and *ADAM19* [100]. Exosomes carrying *circ-ABCC1* from $CD133^+$ cells have the ability to mediate cell stemness and metastasis in CRC [101]. LncRNA *PCAT1*, which is from CRC exosomes, can promote the EMT and liver metastasis of CRC. Because exosome lncRNA *PCAT1* can influence *miR-329-3p* and the activity of the *Netrin-1-CD146* complex in circulating tumor cells (CTCs) [65]. Exosomal-*miR-10a* derived from CRC cells reduced the expression of *IL-6*, *IL-8*, and *IL-1*β in normal human lung fibroblasts (NHLFs), thereby reducing the proliferative and migratory activities of primary NHLFs. This will help us understand the mechanism underlying the process of CRC lung metastasis [66]. Exosomal *miR-1255b-5p* targets human telomerase reverse transcriptase and inhibits its expression in CRC cells, ultimately suppressing tumor progression and liver metastasis of CRC [67]. Exosomal lncRNA *91H* enhances CRC metastasis by modifying *HNRNPK* expression in CRC [49].

3.1.3 Angiogenesis

Angiogenesis is critical for tumor growth, survival, and progression. The process is very complex, including the degradation of the vessel's basement membrane, the activation, proliferation, and migration of vascular endothelial cells, and reconstruction to form new blood vessels and networks [102]. Tumor-derived exosomes are largely involved in this process [103]. This has been demonstrated in the angiogenesis of CRC. For example, exosomal *miR-25-3p*, which is CRC cell-derived, directly targets *KLF2* and *KLF4* and regulates *VEGFR2*, *ZO-1*, *claudin5*, and *occludin* expression in endothelial cells, consequently promoting vascular permeability and angiogenesis [68]. Exosomal *miR-21-5p*, which is secreted by CRC cells, induces angiogenesis and vascular permeability by targeting *KRIT1* [69]. *MiR-1229*, which is derived from the CRC cell exosomes, inhibits the expression of *HIPK2* protein, thus activating the *VEGF* pathway and promoting angiogenesis [70]. Exosomal *Wnt4* derived from CRC cells increases β-*catenin* nuclear translocation in endothelial cells and promotes angiogenesis in CRC [71].

3.1.4 Immune Evasion

Exosomes are important in modulating tumor immune response and have a dual role. They may activate immune responses or exhibit strong pro-tumor immune reactions [17]. Numerous studies have revealed CRC tumor-derived exosomes (CTDEs) can function as mediators of host anti-tumor immune responses and tumor cell immune evasion. For example, *miR-208b* is secreted by colon cancer cells and sufficiently transported to recipient T cells. In T cells, *miR-208b*, which is delivered by exosomes, directly targets *PDCD4* and induces immune evasion [72]. The CRC cell-derived exosomal lncRNA *SNHG10s* can be taken up by NK cells and suppress the function of NK cells by upregulating *INHBC* expression. It has been suggested that exosomal lncRNA *SNHG10* could lead to the inhibition of NK cells, ultimately contributing to immune escape [73]. Exosomes containing *Lnc-HOXB8-1:2* are secreted by neuroendocrine differentiated CRC cells, and *Lnc-HOXB8-1:2* from exosomes competitively binds *hsa-miR-6825-5p* as ceRNA relieves the inhibitory effect of *hsa-miR-6825-5p* on *CXCR3* expression, upregulates its expression, and then leads to TAM infiltration and M2 polarization, and promotes immune evasion of CRC [74]. *CRNDE-h*, which is derived from tumor cells, could inhibit ubiquitination and degradation of *ROR*γt and promote Th17 cell differentiation in CRC [75]. CRC stem cell-derived exosomes (CRCSC-exos) deliver *miR-17-5p* to CRC cells. The high expression of *miR-17-5p* in CRCSC exosomes promotes tumor cell growth by promoting *PD-L1* inhibition of *SPOP* and inhibits the anti-tumor immunity of CRC [76]. Tumor-derived *HOTAIR* could bind to *PKM2* and inhibit its ubiquitination degradation, leading to the activation of *STAT3* and expression of *PDL1*, thereby polarizing B cells toward a regulatory feature and suppressing $CD8^+$ T cell activity [77].

3.1.5 TME Remodeling

The tumor microenvironment (TME) is a complex internal environmental system around tumor cells, which plays an essential role in tumorigenesis. CTDEs in the TME are essential in the formation and reprogramming of the TME. For example, *miR-146a-5p* and *miR-155-5p* contained in CRC cell exosomes can be secreted by CRC cells and taken up by the cancer-associated fibroblasts (CAFs). Then, they may activate CAFs through *JAK2-STAT3/NF-*κB signaling. Reciprocally, the activation of CAFs may further facilitate the invasion of CRC cells [78]. CRC cell-derived exosomal *HSPC111* can be engulfed by CAFs. In CAFs, it may phosphorylate *ACLY* and promote the expression of *acetyl-CoA*. *Acetyl-CoA* accumulation further increases *H3K27* acetylation and promotes *CXCL5* expression in CAFs. Interestingly, *CXCL5* from CAFs can reinforce exosomal *HSPC111* excretion from CRC cells and promote liver metastasis via the *CXCL5-CXCR2* axis [79]. Exosomal *ANGPTL1* derived from CRC cells is mainly taken up by Kupffer cells (KCs). Then, *ANGPTL1* can downregulate *MMP9* levels by inhibiting the *JAK2-STAT3* signaling pathway in KCs [80]. Tumor exosomal

tri-phosphate RNAs sustain neutrophil survival by inducing the expression of *IL-1β* through a pattern recognition-*NF-κB* signaling axis. CRCSC-secreted *CXCL1* and *CXCL2* then attract CRCSC-primed neutrophils to promote tumorigenesis of CRC cells via *IL-1β* [81]. CRC cell-derived exosomes containing *miR-10b* can be transferred to fibroblast cells and activate fibroblasts to become CAFs via the *PI3K/Akt* pathway [82]. Studies also revealed that CRC tumor-derived exosomes contribute to generating phenotypically and functionally distinct subsets of CAFs by reprogramming their proteome and may facilitate tumor progression [77]. Exosomes that carry *miR-203* can be secreted from CRC cells, and they can be swallowed by monocytes. In monocytes, *miR-203* can promote the expression of M2 markers, suggesting that *miR-203* may facilitate the differentiation of monocytes to M2- TAMs [83].

3.1.6 Metabolic Reprogramming

Metabolic reprogramming is an adaptive mechanism that enables tumor cells to regulate the flow of their energy to meet their needs for rapid growth. It is manifested by an increase in glucose uptake and an enhancement of glycolysis under aerobic conditions, as well as high production of lactate. These metabolic changes are also known as the "Warburg effect" [104]. A growing number of studies have shown that exosomes can mediate metabolic reprogramming in cancer [105]. As in CRC, *hsa-miR-101-3p*, which is derived from CRC cell exosomes, is associated with metabolic reprogramming in CRC by targeting *HIPK3* [84]. Moreover, mutant *KRAS* exosomes are able to cause a Warburg-like effect on recipient colonic epithelial cells [85].

3.1.7 Therapy Resistance

It has been demonstrated that the delivery of exosomal cargos between different cancer cells is associated with tumor drug resistance [106]. Exosomes are used as carriers for cell-to-cell communication in the tumor microenvironment, however; drug-resistant tumor cells can also use this property to develop resistance to sensitive cells [107]. Therapy-resistance mechanisms mediated by CTDEs are summarized as follows: *hsa_circ_0005963* is involved in chemoresistance in CRC. The exploration of underlying mechanisms showed that *hsa_circ_0005963* could be a sponge for *miR-122* [86]. Tumor-secreted *miR-208b* directly targets *PDCD4* and promotes Treg expansion, and it may be associated with a decrease of oxaliplatin (OX)-based chemosensitivity in CRC [72]. It is also demonstrated that exosomes from RKO/R cells are able to promote acquired 5-FU resistance in CRC, which is mainly related to *p-STAT3* contained in the exosomes [87]. *Circ_0000338* is present in exosomes and improves the chemoresistance of CRC cells by targeting *miR-217* and *miR-485-3p* [88]. Exosome *miR-46146* can be an important promoter of OX resistance by targeting *PDCD10* and may be a potential target for OX resensitization by CRC cells [89]. *MiR-19b* can be present in exosomes secreted by CRC cells. By delivering *miR-19b*, CRC-derived exosomes enhance the radiation resistance and stemness characteristics of CRC cells. Accordingly, *miR-19b* inhibition can enhance the efficacy of radiotherapy and reduce the stemness characteristics of CRC, suggesting that *miR-19b* inhibition may be a promising strategy for sensitization of CRC cells to radiotherapy [90]. Exosomal circ-*FBXW7* can improve the chemoresistance of CRC to OX by direct binding to *miR-128-3p*, which provides a promising treatment strategy for patients with OX-resistant CRC [91]. Exosomal *circATG4B* plays an important role in chemoresistance in CRC. The underlying mechanisms show that it can competitively bind to *TMED10*, prevent *TMED10* from binding to *ATG4B*, and induce increased autophagy, ultimately promoting chemotherapy resistance [108]. Exosomal long non-coding RNA *HOTTIP* derived from mitomycin-resistant CRC cells can be transferred into the parental cells and increase the resistance of CRC cells to mitomycin via impairing *miR-214*-mediated degradation of *KPNA3* [92].

3.2 Non-Tumousr-Derived Exosomes in CRC

Although tumor cells are the main cells in the tumor microenvironment (TME), there are also many other cells, such as fibroblasts, immune cells, endothelial cells, etc. [109]. Exosomes secreted by non-CRC cells in the TME may also affect the fate of CRC cells. Here, we summarize the functions and mechanisms of non-tumor-derived exosomes in CRC (Fig. 4; Table 2, Ref. [110–134]).

For example, CAFs are the main stromal cells in TME. CAFs can transfer exosomes that are rich in *miR-92a-3p* directly to CRC cells and increase the expression of *miR-92a-3p* in CRC cells significantly. In CRC cells, *miR-92a-3p* directly targets *FBXW7* and *MOAP1*, ultimately promoting the stemness, EMT, metastasis, and chemotherapy resistance of CRC cells [110]. CAFs can deliver *H19* in exosomes to CRC cells, promoting the stemness and resistance of CRCs. Mechanistically, *H19* activates the *β*-catenin pathway by serving as a competing endogenous RNA sponge of *miR-141*, which could inhibit the stemness and chemoresistance of CRC cells after delivery to CRC cells [111]. CAFs-derived exosomes contain a large number of *miR-93-5p*, which can promote tumor growth in irradiated nude mice [112]. Exosomal *LINC00659* could be secreted by CAFs and taken up by CRC cells. Then, it could target the miR-342-3p/ANXA2 axis and promote cell proliferation, invasion, and migration of CRC [113]. Exosomal *circEIF3K* derived from CAFs promotes the progression of CRC via *miR-214/PD-L1* axis [114]. CAFs-derived exosomes contain *miR-181d-5p*, which is associated with 5-FU sensitivity. It has been demonstrated that *miR-181d-5p* inhibits 5-FU sensitivity through the *METTL3/miR-181d-5p/NCALD* axis in CRC cells [115]. CAFs-derived exosome *miR-181b-3p* promotes the occur-

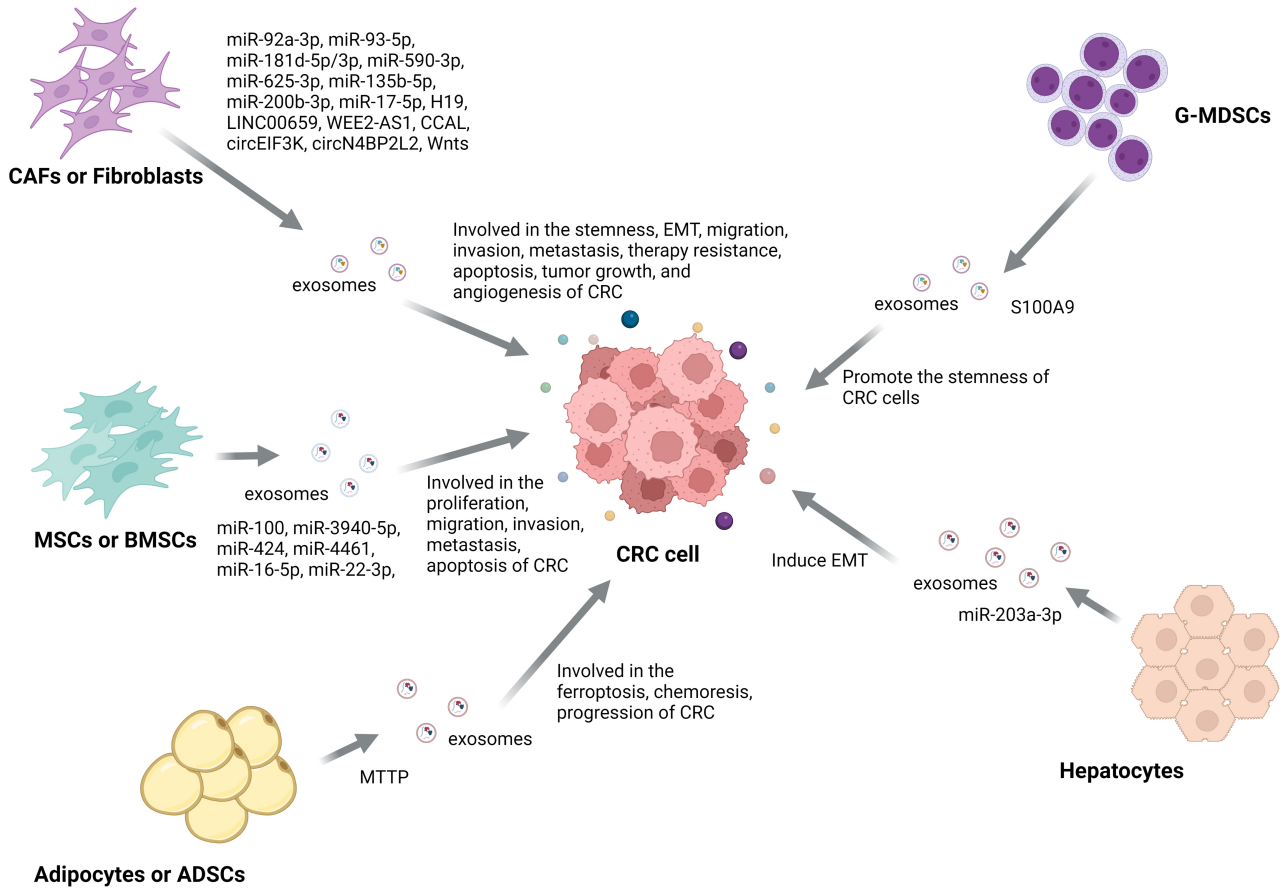

Fig. 4. The Mechanism of non-tumor-derived exosomes function in CRC. Exosomes derived from non-CRC cells can transport their cargo to CRC cells and affect most pathological processes in CRC, including stemness, EMT, migration, invasion, metastasis, angiogenesis, apoptosis, tumor growth, and therapy resistance.

rence and development of CRC by regulating *SNX2* expression [116]. CAFs-secreted exosome *circN4BP2L2* promotes the CRC cell stemness and oxaliplatin resistance through *EIF4A3/PI3K/AKT/mTOR* pathway [117]. CAFs can transmit *miR-590-3p* to CRC cells through exosomes. In CRC cells, *miR-590-3p* enhances the radioresistance of CRC by regulating the *CLCA4*-dependent PI3K/Akt signaling pathway [118]. CAFs exosomes are directly swallowed by CRC cells, and *miR-625-3p* in exosomes is released and may inhibit the *CELF2/WWOX* pathway after entering CRC cells, thereby promoting the migration, invasion, EMT and chemotherapy resistance of CRC cells [119]. CAFs-derived exosomes upregulate *microRNA-135b-5p* to promote CRC cell growth and angiogenesis by inhibiting *TXNIP* [120]. After entering CRC cells, *WEE2-AS1* in the exosomes of CAFs can promote the degradation of *MOB1A*, thereby inhibiting the *Hippo* pathway and promoting the occurrence and progression of CRC tumors [121]. Hypoxia can lead to the loss of *miR-200b-3p* in the exosomes of CAFs, thereby reducing the sensitivity of CRC cells to 5-FU [122]. CAFs-exosomes show higher expression of *miR-17-5p* than normal fibroblasts-exosomes and can deliver exosomal *miR-17-5p* from parental CAFs to CRC cells. Further studies confirm that that *miR-17-5p* directly target *RUNX3* 3'-UTR to affect CRC metastasis. *RUNX3* interacts with the *MYC* proto-oncogene, and both *RUNX3* and *MYC* bind to the promoter of *TGF-β1* on 1005-1296 base pairs, thereby activating the *TGF-β* signaling pathway and promoting tumor progression [123]. LncRNA *CCAL* is transferred from CAFs to the cancer cells via exosomes and promotes oxaliplatin resistance of CRC cells. Mechanistically, *CCAL* interacts directly with mRNA stabilizing protein *HuR* and promoting the expression of *β-catenin* [124]. Exosomes from the normal fibroblasts also influence CRC cells. For example, Exosomal Wnts derived from fibroblasts can induce the differentiation of cancer cells to promote chemoresistance in CRC [125].

Exosomes from mesenchymal stem cells (MSCs) are closely related to the therapeutic efficacy of MSCs. After being ingested by CRC cells, MSC exosomes can exert their effects through the *miR-100/mTOR/miR-143* axis in CRC cells, inhibiting the proliferation, migration, invasion, and metastasis of CRC cells and inducing CRC cell apoptosis. It suggests that MSC-exosome treatment and *miR-100* restoration might be considered potential therapeutic strategies for CRC [126]. MSC-exosomal *miR-3940-5p* inhibits

the growth, metastasis, invasion, and EMT of CRC cells by targeting *ITGA6* and the following *TGF-β1* inactivation [127]. The exosomes produced by bone marrow mesenchymal stem cells (BMSCs) contain abundant *miR-4461*. After being taken up by CRC cells, miR-4461 can directly target *COPB2*, leading to *COPB2* downregulation and inhibiting the migration and invasion of CRC cells [128]. Inhibited exosomal *miR-424* from BMSCs inhibited malignant behaviors of CRC cells by targeting *TGFBR3*, thus suppressing the progression of CRC [129]. BMSCs exosomes contain *microRNA-16-5p*, and exosomes containing *microRNA-16-5p* are swallowed by CRC cells, which inhibit the proliferation, migration, and invasion of CRC cells and promote apoptosis of CRC cells [130]. Exosomes derived from MSCs are rich in *miR-22-3p*, which inhibits CRC cell proliferation and invasion by regulating RAP2B and *PI3K/AKT* pathways, suggesting the potential of hBMSCs-exo-*miR-22-3p* for the treatment of CRC in the future [131].

Some other cells may also affect the fate of CRC cells. For example, Granulocytic Myeloid-derived suppressor cells (G-MDSCs) promote the stemness of CRC cells through exosomal *S100A9* [132]. Adipocyte-derived exosomal *MTTP* could suppress ferroptosis and promote chemoresistance in CRC [133]. *MiR-203a-3p* derived from hepatocyte exosomes increases the expression of *E-cadherin* in CRC cells and inhibits *Src* expression, which in turn leads to a decrease in the invasion rate of CRC cells [134].

4. The Potential Clinical Value of Exosomes in CRC

Due to their unique properties, exosomes contribute to many aspects of precise tumor diagnosis and treatment, including predicting prognosis and drug efficacy, dynamic monitoring, and precisely targeted drug delivery [14].

4.1 Exosomes in CRC Diagnosis and Prognosis

Because of the various cargos in the exosomes and the typical features on the surface of exosomes, they can reflect the status of their parent cells. Thus, exosomes have emerged as a platform with potentially broader and complementary applications to be used in the field of liquid biopsy for the diagnosis, prognostic analysis, and monitoring of cancer [135]. In this manuscript, we summarized the exosomes used in the diagnosis and prognosis of CRC (Table 3, Ref. [55,58,72,75,136–166]).

Exosomal LncRNA *RPPH1* levels in blood plasma are higher in untreated CRC patients but lower after tumor resection. It displayed a better diagnostic value (AUC = 0.86) compared to *CEA* and *CA199* and could serve as a potential target for therapy and diagnosis in CRC [55]. The *miR-208b* derived from exosomes of CRC cells can promote Treg amplification by regulating *PDCD4*, and it has the ability to reduce the sensitivity of oxaliplatin-based chemotherapy in CRC. These research results suggest that the exosomal *miR-208b* can serve as a biomarker for predicting oxaliplatin treatment response and may become a new target for immunotherapy [72]. Exosomal *miR-221/222* promotes CRC progression and may serve as a novel prognostic marker and therapeutic target for CRC with liver metastasis [58]. By deep sequencing, it has been demonstrated that miR-7641 has the potential to be a candidate for the non-invasive and specific molecular markers for CRC diagnosis and prognosis [167]. Exosome-delivered *FZD10* increases *Ki-67* expression via *Phospho-ERK1/2* and may be a promising novel prognostic and diagnostic biomarker for CRC [168]. Elevated plasma $GPC1^+$ exosomes and decreased plasma *miR-96-5p* and *miR-149* expression may be specific markers for the diagnosis of CRC and targets for the treatment of CRC. Compared with the healthy control group, the percentage of $GPC1^+$ exosomes in tumor tissue and plasma and the expression of *GPC1* protein in exosomes in CRC patients before surgery were significantly increased. However, *miR-96-5p* and *miR-149* expression in tumor tissue and plasma and $GPC1^+$ exosomes in CRC patients were significantly reduced compared to healthy controls [169]. The expression of exosomal *miR-377-3p* and *miR-381-3p* are decreased in CRC patients; they can serve as circulating biomarkers of diagnosis for CRC [136]. *CircCOG2* is associated with poor prognosis and can be used as a therapeutic target for CRC [137]. Circulating or tissue-based *miR-1539* derived from CRC cells may be used as a novel potential biomarker for CRC screening, as well as a predictor of poor clinicopathological behavior in tumors [138]. Circulating exosomal *miR-150-5p* and *miR-99b-5p* derived from CRC cells may be considered diagnostic biomarkers for CRC [139]. *Hsa-miR-3937*, contained in tumor-originated exosomes, is a potential and effective liquid biopsy marker for CRC detection and therapy [140]. The downregulation of exosomal *miR-548c-5p* in serum predicts poor prognosis in patients with CRC, and thus it may be a critical biomarker for CRC diagnosis and prognosis [141]. Circulating exosomal *CPNE3* may be a diagnostic and prognostic biomarker for CRC [142]. Plasma exosomal *miRNA-139-3p* is decreased in CRC and may act as a novel biomarker for early diagnosis and metastasis monitoring in CRC [143]. CRC cell-derived exosomes are rich in *miR-424-5p*, and *miR-424-5p* is secreted into peripheral blood through exosomes. The circulating exosomes *miR-424-5p* can be used as a marker for early diagnosis of CRC [75]. Exosomal *miR-320d* could significantly distinguish metastatic from non-metastatic CRC patients and be a biomarker for metastatic CRC [144]. The expression of LncRNA *GAS5* and *miR-221* in CRC tissue, patient plasma, and exosomes can be independent prognostic factors for CRC [145]. Studies have revealed that the expression of *hsa-circ-0004771* in circulating exosomes in CRC patients is significantly upregulated, which is expected to become a new biomarker for colorectal cancer diagnosis [146]. After the *circ_0006174*-rich ex-

Table 2. The function and mechanism of non-tumor-derived exosomes in CRC.

Type	Molecule	Source	Function	Target	Ref.
miRNA	*miR-92a-3p*	CAFs	Promote the stemness, EMT, metastasis, and chemotherapy resistance of CRC cells	*FBXW7, MOAP1*	[110]
	miR-93-5p	CAFs	Against radiation-induced apoptosis	*FOXA1*	[112]
	miR-181d-5p	CAFs	Inhibit 5-FU sensitivity	*NCALD*	[115]
	miR-181b-3p	CAFs	Promote the occurrence and development of CRC	*SNX2*	[116]
	miR-100	MSCs	Suppress proliferation, migration, invasion, and metastasis and induce apoptosis	*mTOR*	[126]
	miR-3940-5p	MSCs	Inhibit the growth, metastasis, invasion, and EMT of CRC cells	*ITGA6*	[127]
	miR-590-3p	CAFs	Enhance radioresistance in CRC	*CLCA4*	[118]
	miR-625-3p	CAFs	Promote migration, invasion, EMT, and chemotherapeutic resistance in CRC cells	*CELF2*	[119]
	microRNA-135b-5p	CAFs	Promote CRC cell growth and angiogenesis	*TXNIP*	[120]
	miR-424	BMSCs	Promote progression of CRC	*TGFBR3*	[129]
	miR-200b-3p	CAFs	Increase sensitivity to 5-FU	*HMGB3*	[122]
	miR-4461	BMSCs	Inhibit migration and invasion	*COPB2*	[128]
	microRNA-16-5p	BMSCs	Inhibit proliferation, migration, and invasion, while promoting apoptosis	*ITGA2*	[130]
	miR-203a-3p	hepatocyte	Induce EMT	*Src*	[134]
	miR-17-5p	CAFs	Contribute to tumor progression	*RUNX3*	[123]
	miR-22-3p	BMSCs	Suppress CRC cell proliferation and invasion	*RAP2B*	[131]
LncRNA	*H19*	CAFs	Promote the stemness and chemoresistance of CRC	*miR-141*	[111]
	LINC00659	CAFs	Promote CRC cell proliferation, invasion, and migration	*miR-342-3p*	[113]
	WEE2-AS1	CAFs	Facilitate tumorigenesis and progression	*MOB1A*	[121]
	CCAL	CAFs	Promote oxaliplatin resistance of CRC cells	*HuR*	[124]
circRNA	*circEIF3K*	CAFs	Promote the progression of CRC	*miR-214*	[114]
	cricN4BP2L2	CAFs	Promote the CRC cell stemness and oxaliplatin resistance	*EIF4A3*	[117]
Others	*MTTP*	Adipocyte	Suppress ferroptosis, promote chemoresistance	*PRAP1*	[133]
	S100A9	G-MDSCs	Promote the stemness of CRC cells		[132]
	Wnts	Fibroblasts	Induce the dedifferentiation of cancer cells to promote chemoresistance		[125]

osomes enter CRC cells, the DOX resistance of CRCs is improved through the *miR-1205/CCND2* axis. Therefore, exosome *circ_0006174* is expected to become a biomarker for the diagnosis of chemotherapy resistance in CRC [147]. Serum exosomal *miR-874* is significantly downregulated in CRC patients and has been negatively associated with distant metastasis, lymph node metastasis, differentiation, and advanced TNM stage. Thus, serum exosomal *miR-874* may be a statistically significant independent prognostic factor for CRC patients [148]. It is also demonstrated that exosomal *FGB* and *β2-GP1* can be used as significant diagnostic efficacy for early CRC by using comprehensive proteomics analyses [149]. Circulating exosomes *miR-17-5p* and miR-92a-3p may be non-invasive prognostic markers in patients with CRC, being either primary or metastatic CRC [150]. Exosome lncRNAs *FOXD2-AS1*, *NRIR*, and *XLOC_009459* are promising biomarkers for diagnosing CRC, especially early-stage CRC [151]. Plasma exosomal *miR-21* levels are a useful biomarker for the prediction of recurrence and poor prognosis in CRC patients with TNM stage II, III, or IV [152]. *MiR-6869-5p* may play a cancer-suppressing role in CRC, and serum exosome *miR-6869-5p* is a promising circulating biomarker for predicting the prognosis of CRC [153]. Serum exosomal *miR-122* is a novel potential diagnostic and prognostic biomarker in CRC patients with liver metastasis (LM) [154]. Serum exosome circ-PNN may be a new biological marker for CRC detection, with non-invasive characteristics, and may play an important role in the tumorigenesis of CRC [155]. Exosomal *UCA1* is detectable and stable in the serum of CRC patients. Moreover, circulating exosomes containing *UCA1* can predict the clinical outcome of treatment with cetuximab in CRC patients [156]. Exosomal *miR-150* can be used as a marker for the prognosis of CRC patients after surgical resection, and its low expression predicts poor prognosis after surgery. Therefore, exosome *miR-150* may be a

Table 3. The Clinical Potential of Exosomes "cargos" in CRC.

Type	Exosomes	Clinical Potential	Ref.
miRNA	*miR-208b*	A predictive biomarker for oxaliplatin-based therapy response	[72]
	miR-221/222	A prognostic marker and potential therapeutic target for CRC with liver metastasis	[58]
	miR-7641	A molecular biomarker for diagnosis and prognosis of CRC	[167]
	miR-96-5p and miR-149	A biomarker for early detection of CRC	[169]
	miR-377-3p and miR-381-3p	Circulating biomarkers for diagnosis of CRC	[136]
	miR-1539	A potential biomarker for screening and a predictor of poor clinicopathological behavior in CRC	[138]
	miR-150-5p and miR-99b-5p	Serve as diagnostic biomarkers for CRC	[139]
	miR-3937	A potential liquid biopsy marker for CRC	[140]
	miR-548c-5p	A critical biomarker for CRC diagnosis and prognosis	[141]
	miRNA-139-3p	A biomarker for early diagnosis and metastasis prediction in CRC	[143]
	miR-424-5p	A biomarker for early diagnosis in CRC	[75]
	miR-320d	A biomarker for metastatic CRC	[144]
	miR-221	An independent prognostic factor for CRC	[145]
	miR-874	An independent prognostic factor for overall survival of CRC patients	[148]
	miR-17-5p and miR-92a-3p	A prognostic biomarker for primary and metastatic CRC	[150]
	miR-21	A predictor of recurrence and poor prognosis in CRC	[152]
	miR-6869-5p	A circulating biomarker for the prognosis of CRC	[153]
	miR-122	A potential diagnostic and prognostic biomarker for CRC with liver metastasis	[154]
	miR-150	A potential prognostic factor and treatment target for CRC	[157]
	miR-150-5p	A novel non-invasive biomarker for CRC diagnosis and prognosis	[159]
	miR-125b-5p	Be potentially correlated with a more aggressive CRC phenotype	[161]
	miR-92b	A promising biomarker for early detection of CRC	[162]
	miR-126, miR-1290, miR-23a, and miR-940	Potential biomarkers for early diagnosis of CRC	[164]
	microRNA-125b	A biomarker of resistance to mFOLFOX6-based chemotherapy in CRC	[165]
	miR-181b, miR-193b, miR-195, and miR-411	A predicter for lymph node metastasis in T1 CRC patients	[166]
LncRNA	*RPPH1*	A potential biomarker for diagnosis and therapy in CRC	[55]
	GAS5	An independent prognostic factor for CRC	[145]
	FOXD2-AS1, NRIR, and XLOC_009459	Biomarkers for the diagnosis of CRC	[151]
	UCA1	A predicter for therapeutic efficacy of cetuximab in CRC patients	[156]
	CCAT2	A potential predictor of CRC	[163]
circRNA	*circCOG2*	A biomarker for poor prognosis and a therapeutic target for CRC	[137]
	circ-0004771	A novel potential diagnostic biomarker of CRC	[146]
	circ_0006174	A biomarker for the diagnosis of chemoresistance in CRC	[147]
	circ-PNN	A potential biomarker for the detection of CRC	[155]
Others	*FZD10*	A biomarker for prognosis and diagnosis of CRC	[168]
	GPC1	A biomarker for early detection of CRC	[169]
	CPNE3	A diagnostic and prognostic biomarker for CRC	[142]
	FGB and β2-GP1	Biomarker for diagnostic efficacy of early CRC	[149]
	QSOX1	A marker for early diagnosis and non-invasive risk stratification in CRC	[158]
	KRAS	A predictor for outcome in CRC patients with metastasis	[160]

prognostic factor and potential therapeutic target for CRC [157]. Exosome-derived *QSOX1* is a new promising marker for early diagnosis and non-invasive risk stratification of CRC [158]. Serum exosomal *miR-150-5p* is expressed differently between healthy people and CRC patients and is expected to be a potential molecular marker for the diagnosis and prognosis of CRC [159]. *KRAS* mutations are very common in CRC, *KRAS* mutations are manifested in exosomes, and plasma exosome *KRAS* mutation status predicts the prognosis of patients with metastatic CRC [160].

The higher the expression of *miR-125b-5p* in plasma exosomes, the stronger the CRC aggressiveness, suggesting that *miR-125b-5p* in plasma exosomes may be related to the phenotype of CRC aggressiveness [161]. Exosome-derived *miR-92b* is down-regulated in the plasma of CRC patients and can be used as a molecular marker for early diagnosis of CRC [162]. Circulating *CCAT2* is present in exosomes, protected by exosomes, and can serve as a potential predictor of CRC [163]. In CRC cells, miRNAs can be encapsulated into exosomes and secreted outside the cell, regardless of intracellular miRNA expression. Among these miRNAs, serum exosomes *miR-126*, *miR-1290*, *miR-23a*, and *miR-940* are novel potential molecular markers for early diagnosis of CRC [164]. In patients with advanced and recurrent CRC, plasma exosome *microRNA-125b* can be used as a molecular marker for detecting *mFOLFOX6*-based chemotherapy resistance [165]. A group of miRNAs which includes *miR-181b*, *miR-193b*, *miR-195*, and *miR-411*, is able to detect lymph node metastasis in the exosomal *vs.* cell-free component. This suggests that exosomal miRNA-based liquid biopsy features can strongly identify invasive submucosal CRC (T1 CRC) patients at risk of lymph node metastasis in the preoperative setting [166].

4.2 Exosomes in CRC Clinical Transformation

Because of the properties and functions of exosomes, they can be designed for drug or functional nucleic acid delivery [170] and have the therapeutic potential to be used in the treatment of CRC. For example, engineered exosomes have been used to simultaneously deliver the anticancer drug 5-FU and the *miR-21* inhibitor oligonucleotide (miR-21i) to *Her2*-positive cancer cells. The results revealed that systematic administration of exosomes loaded with 5-FU and *miR-21i* in tumor-bearing mice showed significant anti-tumor effects in colon cancer [171]. Studies have shown that the expression of *PGM5* antisense RNA 1 (*PGM5-AS1*) in colon cancer is induced by *GFI1B*. *PGM5-AS1* prevents colon cancer cells from proliferating, migrating, and acquiring oxaliplatin tolerance, and engineered exosomes that co-deliver *PGM5-AS1* and oxaliplatin can reverse colon cancer resistance [172]. MiR-506-3p delivered to CRC cells via exosomes reduces CRC proliferation and induces apoptosis, suggesting that delivery of *miR-506-3p* to CRC cells via exosomes may become a novel diagnosis and treatment method for CRC [173]. Tumor-derived exosomes (TEXs) may induce beneficial anti-tumor immune responses, and TEXs have shown certain beneficial anti-tumor properties in addition to miRNA delivery functions, suggesting that the introduction of TEX-*miR-34a* may be a new promising approach for combination therapy for CRC [174]. Studies have shown that dendritic cells are loaded with exosomes from cancer stem cell-rich spheroids, which may be a new potential immunotherapy approach [50]. It has been reported that the ascites-derived exosomes (Aex), in combination with the granulocyte-macrophage colony-stimulating factor (GM-CSF), could be used in the immunotherapy of CRC. The phase I clinical trial suggested that AEX combined with GM-CSF immunotherapy for advanced CRC is feasible and safe and may be an alternative to immunotherapy for advanced CRC [175].

Although exosomes have been considered promising emerging therapeutic options and tumor neo-antigen drug delivery tools and carriers in tumor precision therapy, there are still many issues waiting to be resolved. Nowadays, exosomes can be isolated and purified by ultracentrifugation, density gradient centrifugation, polymer precipitation, ultrafiltration, and size exclusion chromatography; however, flexible and fast detection platforms are still lacking. Moreover, how to load exosomes with specific cargo still need to be explored. Because few studies have focused on the fusion-based loading methods present, their detrimental effects on recipient cells remain unclear [14].

5. Conclusions and Prospects

Exosomes are derived from the endosomal pathway of nearly all cells and may be considered a cell-to-cell system in the human body that can mediate near- and long-distance intercellular communication and affect various aspects of cell biology. They are involved in different physiological and pathological processes, such as the communication of the nervous system, reproduction and development, inflammatory responses, cardiovascular diseases, and cancer development.

CRC is one of the most highly malignant tumors worldwide. Numerous studies have revealed that exosomes play important roles in tumor growth, invasion, metastasis, angiogenesis, immune evasion, TME remodeling, metabolic reprogramming, therapy resistance, and some other processes of CRC. Because of these features and functions of exosomes, they may be used in the fields of diagnosis, prognosis, and treatment of CRC. We have reviewed the current state of studies focused on the exosomes in CRC. We have compared the effects of tumor-derived and non-tumor-derived exosomes on the processes of CRC, summarized the clinical value of various types of exosomal cargos, and presented the potential of exosomes to be used in the clinical transformation process.

However, there are still many issues waiting to be resolved before exosome-based therapy can be used in the clinical treatment of CRCs. First, it is still a problem to obtain a large number of exosomes quickly so far. The isolation and purification of exosomes can be realized by the following methods, such as separation based on the size of density or particle, sedimentation or phase, affinity, microfluidic systems, or thermophoretic enrichment. However, the efficiency, quantity, and quality of exosomes separated by different separation methods are different, and there is still a lack of unified methods that can quickly and effectively obtain exosomes. Moreover, how to equip exosomes with specific drugs is also a problem. There are two

methods for loading exosomes with drug, endogenous and exogenous. The two methods both have their own disadvantages; the endogenous method is not accurate in quantifying the specific substances in the exosomes, while the loading efficiency is not high using the exogenous methods. Thus, how to equip exosomes with specific drugs is also a question that needs to be resolved. Furthermore, the long-term efficacy and safety of using exosomes in the treatment of CRC remain unclear. Therefore, there is a need for comprehensive clinical studies or trials of exosomes used in CRC. It is possible that with technological developments and further clinical trials, exosomes will be a real emerging tool for the "cell-free" treatment of CRC.

Author Contributions

Conceptualization: JH, YH; writing - original draft preparation: JH, SM, YZ, BW, SD, YH; writing – review and editing: JH, YH; visualization: SM, YH; analyzing: YZ, BW, SD; interpreting data from the reviewed literature, JH, SM, YZ, BW, SD; supervision: YH. All authors have read and agreed to the published version of the manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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