

Origin dictates function: The dual roles of exosomes derived from diverse origins in the onset and progression of colorectal cancer (Review)

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Abstract. Globally, colorectal cancer (CRC) ranks third in terms of incidence, while it is the second leading cause of cancer-related mortality. The high incidence and mortality rates of CRC pose a considerable challenge to global human health. Currently, surgical treatment and chemotherapy, which exert unsatisfactory clinical benefits in patients with CRC, are posing major issues in clinical practice, including recurrence, drug resistance and drug toxicity. Therefore, novel treatment approaches for CRC are urgently needed. Emerging evidence has suggested that exosomes carry out a key role in the occurrence and development of CRC, thus attracting considerable attention from researchers. However, exosomes act in a source-dependent manner as exosomes from different sources can exhibit distinct roles in the onset and progression of CRC. The present review systematically summarizes the molecular mechanisms underlying the effects of exosomes from different sources on promoting or inhibiting CRC. Additionally, the potential of exosomes in the diagnosis and treatment of CRC are also discussed, thus providing a foundation for the future application of exosomes in managing CRC.

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1. Introduction

Colorectal cancer (CRC) is a prevalent type of cancer of the digestive system (1). According to the 2022 Global Burden of Disease database, which analyzed data from 204 countries, the global incidence and mortality rates of CRC have increased >100% over the past three decades (2). Notably, epidemiological studies have revealed an increasing trend in CRC incidence and mortality among younger populations, statistical projections indicate that by 2030, ~33% of colorectal cancer cases will occur in individuals <50 years of age (3-5), which is mainly associated with changes in dietary habits, environmental factors and unhealthy lifestyle choices, such as smoking, alcohol consumption and lack of exercise (6-9). In clinical practice, early-stage CRC is commonly treated by surgical resection. However, due to its insidious onset, CRC is often diagnosed at advanced stages, thereby limiting opportunities for effective early intervention (10). For patients with advanced CRC, conventional therapeutic strategies, including chemotherapy, radiotherapy, immunotherapy and targeted therapies, are commonly employed. Although notable advancements have been achieved in these therapeutic modalities in recent years, the prognosis of advanced CRC remains unfavorable, with poor 5-year survival rates. This clinical reality highlights the urgent need for novel treatment approaches (11-13).

Exosomes are membrane-bound microvesicles, ranging from 30-150 nm in diameter, that carry nucleic acids, proteins, lipids and metabolites. These vesicles are widely distributed in various biological fluids and are involved in diverse physiological and pathological processes (14). The heterogeneity of exosomes is determined by their size, cargo composition and cellular origin (15). Exosomes derived from different tissues and cell types exhibit distinct characteristics, which can exert divergent effects on CRC (16). Previous studies have highlighted their therapeutic potential in treating CRC (17-19). However, it has been reported that tumor-derived exosomes

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can promote CRC progression by modulating the activity of diverse molecular pathways (20). Therefore, elucidating the dual roles of exosome subpopulations from different cellular sources in CRC is of clinical importance.

2. The occurrence and metastasis of CRC

The vast majority of CRC arise from colorectal polyps that initially develop into early adenomas. In turn, these adenomas can progress into advanced adenoma, and ultimately, into CRC. This process is commonly caused by gene mutations and typically occurs over a period of 10-15 years. The most commonly mutated genes in CRC include *APC*, *CTNNB1*, *KRAS*, *BRAF*, *SMAD4*, *TGFBR2* and *TP53* (21,22). Mutations in the aforementioned genes can promote the occurrence and metastasis of CRC by disrupting the functions of key signaling pathways, including those of Wnt/ β -catenin, epidermal growth factor/MAPK, phosphoinositide-3 kinase (PI3K) and TGF- β (23,24). Although alterations in the Wnt signaling pathway are commonly associated with CRC progression, subsequent dysregulation of other signaling pathways serve a key role in promoting tumor progression and metastasis (25).

3. Exosomes

Origin and development of exosomes. The field of extracellular vesicle (EV) biology dates to 1946, with Chargaff and West's (26) identification of a thromboplastic factor in hemophilic blood, now considered the first documented EV observation. In 1967, Wolf (27) further characterized these particles in plasma and published their electron micrographs, coining the term 'platelet dust'. Although nomenclature evolved over decades, these entities are now collectively referred to as EVs. Several conventional markers, such as CD9, CD63, CD81, TSG101, Alix, Flotillin-1, heat shock cognate 70 kDa protein, actin, major histocompatibility complex (MHC) I and MHCII are distributed across different EV subtypes, making classification based on surface markers difficult. EVs are commonly classified by size and biogenesis mechanisms into the following three subtypes: Exosomes (diameter, 30-150 nm), microvesicles (diameter, 100-1,000 nm) and apoptotic bodies (diameter, 500-5,000 nm; Fig. 1). The experiments by Harding *et al* (28) and Pan *et al* (29), successively demonstrated that exosomes are formed by budding inwardly through the cytoplasmic membrane and subsequently forming polycystic vesicles. By contrast, microvesicles are released via outward budding of the plasma membrane, while apoptotic bodies arise during programmed cell death, the present review only focuses on exosomes. Between 2000 and 2010, exosomes became a pronounced focus of investigation. A study conducted *in vitro* experiments revealed that exosomes are rich in proteins, lipids and RNA, including mRNA and microRNA, which enables exosomes to mediate diverse biological functions (30). Exosomes are secreted by various cells and are present in almost all body fluids (31), including blood, saliva, urine, cerebrospinal fluid and breast milk. However, exosomes derived from different sources exhibit their own unique advantages and have been associated with the onset of several types of cancer, such as colon cancer (32), bladder cancer (33), ovarian cancer (34) and melanoma (35), all of which have

been confirmed *in vitro*. Exosomes also carry out a notable role in other diseases, such as neurodegenerative diseases, diabetic cardiomyopathy, metabolic disorders and ischemic stroke (36-39). A pivotal advancement occurred in 2011 with the establishment of the International Society for Extracellular Vesicles (ISEV), which accelerated exosome research. In 2014, the ISEV issued seminal guidelines standardizing EV characterization based on biochemical, biological and functional criteria (40). Since then, substantial progress has been made in elucidating exosome biogenesis, refining isolation methodologies and clarifying their biological and mechanistic functions (Fig. 2).

Isolation and extraction of exosomes. Different isolation approaches can substantially affect exosome purity, yield and physicochemical properties (41). Furthermore, the intrinsic heterogeneity of exosomes in size, cargo and function presents challenges for their separation and extraction (42). Therefore, achieving high-purity exosome isolation with high efficiency remains a major technical challenge. Based on research, the present review systematically summarizes the specific separation methods: Ultracentrifugation (43-45), size-based separation (46-48), flush separation (49), polymer precipitation (43,50,51), ultrafiltration (52-54), immunoaffinity capture (55-57) and microfluidics technology (58,59), as well as their respective advantages and disadvantages (Table SI) (43-59).

Ultracentrifugation is currently the most widely used isolation method and is considered the gold standard for exosome separation and extraction (60,61). In 1955, Lathe and Ruthven (62) proposed a size-based separation method, known as size-exclusion chromatography (SEC). SEC offers the key advantage of preserving the natural biological activity of exosomes (63). Cheng *et al* (49) suggested that although the rinsing separation method was simple to operate and cost-effective, it could inevitably lead to the loss of exosomes during processing, thus resulting in a low yield of extracted exosomes. Polymer precipitation represents another commonly used exosome isolation strategy (50). Compared with ultracentrifugation, ultrafiltration can markedly reduce preparation time, while it does not require special equipment, thus it is considered an ideal alternative to traditional ultracentrifugation (64). Immunoaffinity capture technology can enable the specific isolation and extraction of exosomes with high purity and sensitivity (65). The study by Salieb-Beugelaar *et al* (66) demonstrated that microfluidic technology could efficiently separate exosomes through microfluidic systems.

Although several methods have been developed for exosome isolation and extraction, each approach has certain limitations and no approach can simultaneously achieve high efficiency, high purity, operational simplicity and low cost. Consequently, previous studies have increasingly focused on combining multiple methods for exosome isolation and extraction, thus yielding promising results (67,68).

Different sources of exosomes. Exosomes arise from a wide range of biological sources. The present review systematically categorized their sources into the following: i) Normal cells, including mesenchymal stem cells, dendritic cells, neutrophils, natural killer cells, immune cells and macrophages (69-71);

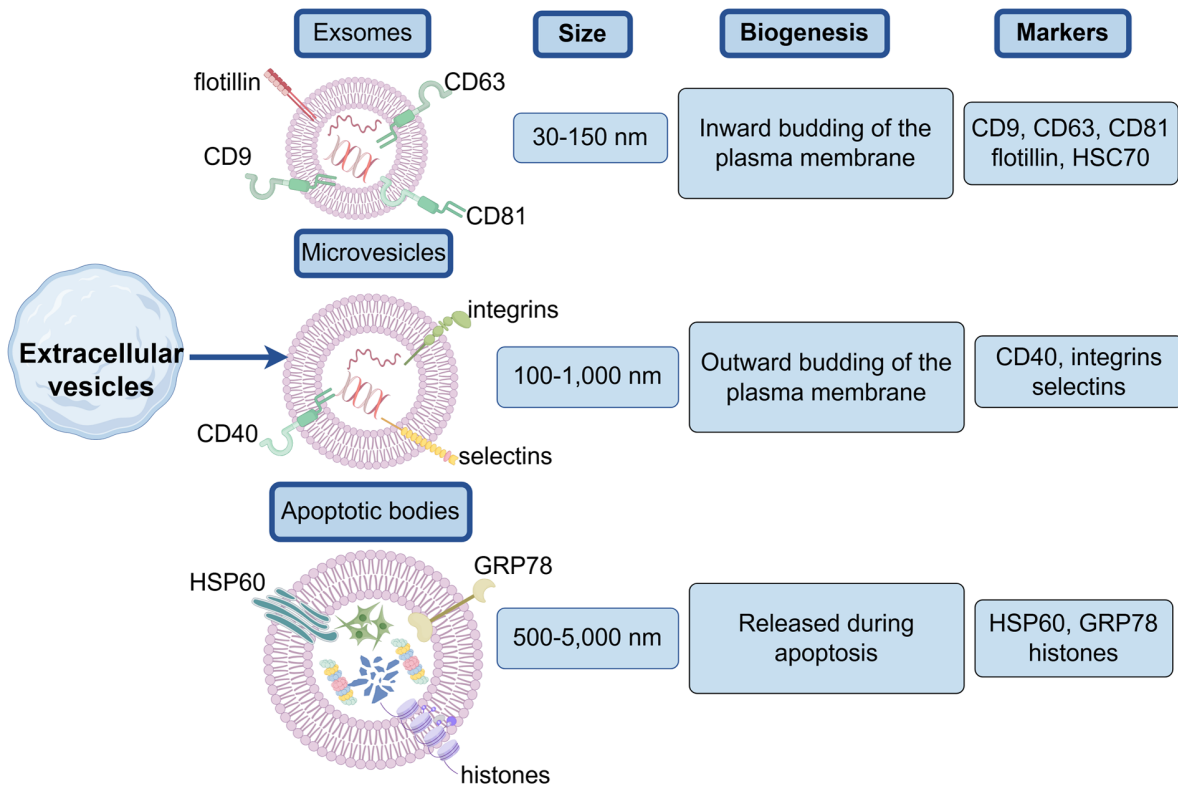


Figure 1. Classification of extracellular vesicles.

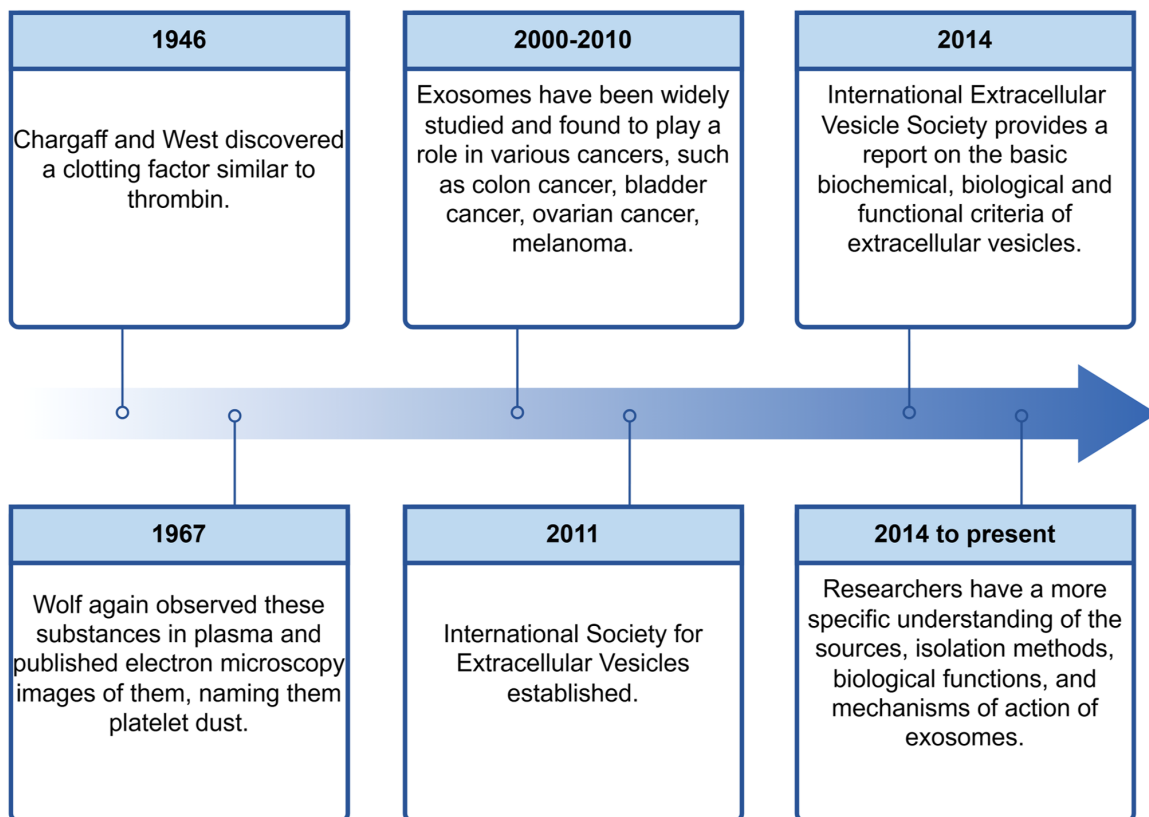


Figure 2. Time line diagram illustrating key events in the origin and development of exosome research.

ii) tumor cells, which have been identified in several types of cancer, such as in hepatocellular carcinoma, ovarian cancer, CRC, breast cancer, gastric cancer, prostate cancer, bladder cancer, melanoma, non-small cell lung cancer,

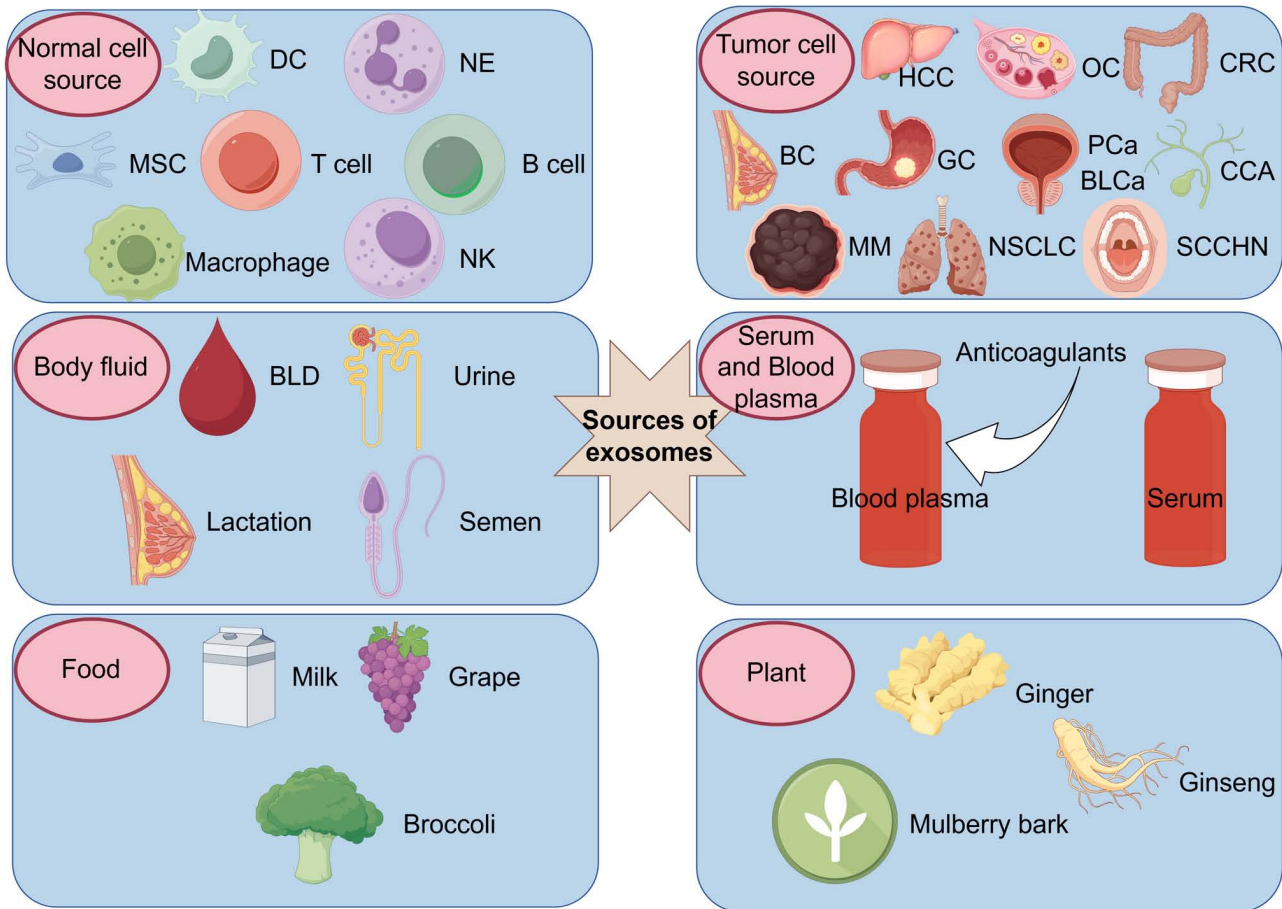


Figure 3. Different sources of exosomes. DC, dendritic cells; NE, neutrophils; MSC, mesenchymal stem cells; NK, natural killer cells; HCC, hepatocellular carcinoma; OC, ovarian cancer; CRC, colorectal cancer; BC, breast cancer; GC, gastric cancer; PCa, prostate cancer; BLCa, bladder cancer; CCA, cholangiocarcinoma; MM, melanoma; NSCLC, non-small cell lung cancer; SCCHN, head and neck squamous cell carcinoma.

cholangiocarcinoma and head and neck squamous cell carcinoma (69,72,73); iii) bodily fluids, including blood, urine, breast milk and semen (74,75); iv) serum/plasma (76-78); v) food sources, such as milk, grapes and broccoli (79,80); and vi) plants, such as ginger, mulberry bark, ginseng and galangal (81-83) (Fig. 3).

4. Dual roles of exosomes from different sources in CRC

Exosomes, as key mediators of intercellular communication, play multifaceted and complex roles in the initiation, progression and metastasis of CRC. Emerging evidence has suggested that exosomes derived from different cellular origins exhibit dual functions in CRC (Fig. 4). Therefore, they can promote tumor growth, invasion and immune evasion. Conversely, they can also suppress tumor growth or enhance chemosensitivity. This functional duality supports the important dependence of exosomal activity in CRC on their cellular source.

In the following section, the bidirectional regulatory mechanisms of exosomes derived from normal cells (Table SII) (84-94), tumor cells (Table SIII) (95-109), blood (Table SIV) (110,111), food (Table SV) (112-114) and plants (Table SVI) (115,116) were systematically summarized, thus providing a theoretical basis for the clinical development of novel diagnostic and therapeutic strategies.

In the study on the effect of exosomes derived from normal cells on CRC, the present review expounds that exosomes from the same source could have different effects on CRC through different mechanisms. For instance, exosomes derived from adipocytes have been reported to inhibit the progression of CRC by delivering microsomal triglyceride transfer protein to suppress lipid reactive oxygen species generation and reduce the susceptibility of cells to ferroptosis (84). Adipocyte-derived exosomes can also target jagged 1 by carrying miR-199b-5p to enhance the radioresistance of CRC cells and promote their proliferation (85). However, the latter cancer-promoting effect has only been verified in *in vitro* cell models to date (85). Its *in vivo* pathological association and potential clinical application still need to be further confirmed in animal models or clinical samples that mimic the human physiological environment more closely. Conversely, multiple studies have suggested that mesenchymal stem cells (MSCs) [such as those derived from bone marrow (B)-MSCs (86-88) and umbilical cord (UC)-MSCs (89,90)], natural killer (NK) cells (91) and dendritic cells (DCs) (92) exhibit good anti-tumor potential in CRC models. The strength of the evidence on which these conclusions are based varies: Among them, the functions of UC-MSCs, NK cells, DC cells and macrophage-derived exosomes have been verified in *in vivo* mouse models (89-94); the mechanism of action of B-MSCs exosomes is currently mainly based on *in vitro* experimental

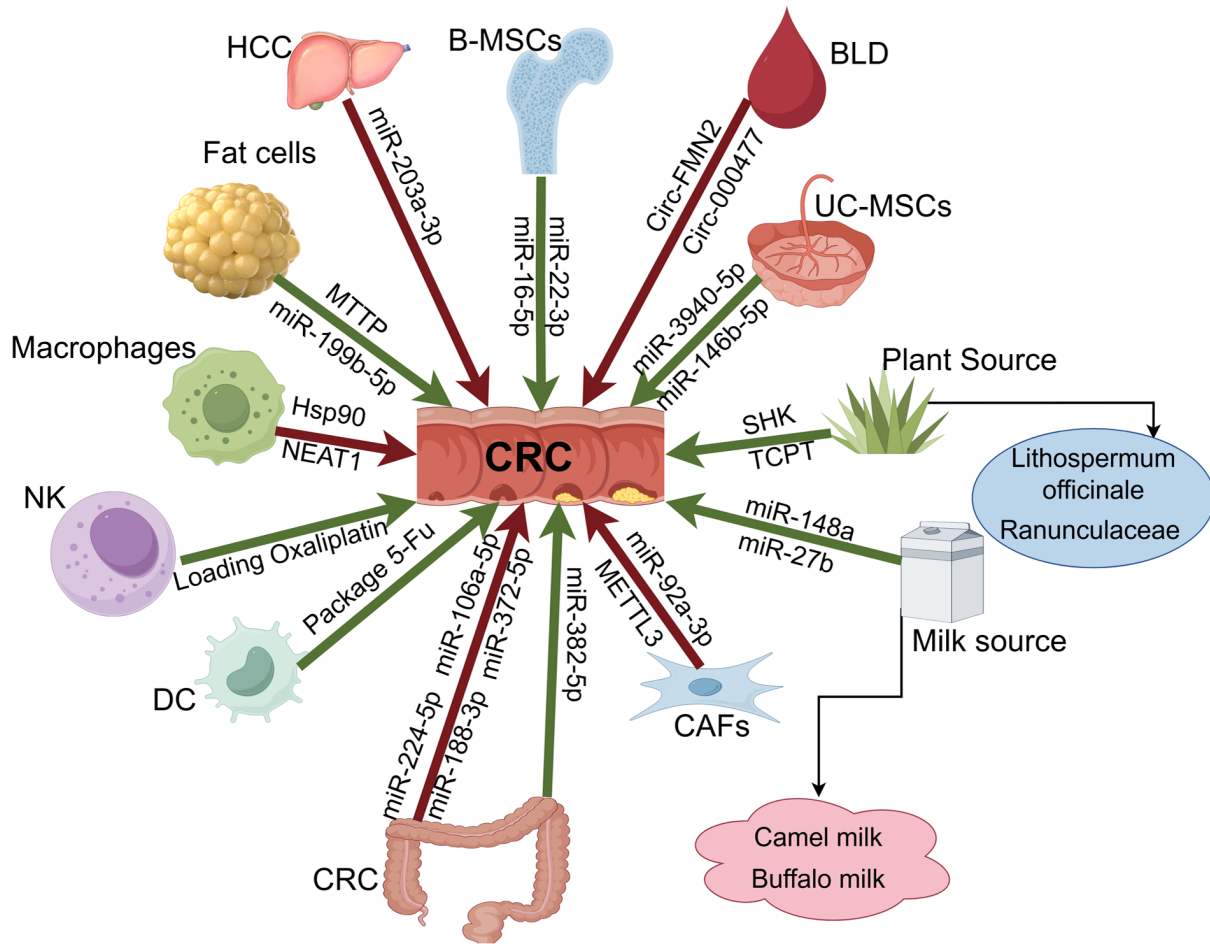


Figure 4. Dual roles of exosomes from different sources in CRC. Red arrows indicate tumor promoters, while green arrows indicate tumor suppressors. B-MSCs, bone marrow mesenchymal stem cells; UC-MSCs, umbilical cord-derived mesenchymal stem cells; HCC, hepatocellular carcinoma; NK, natural killer cells; DC, dendritic cells; CRC, colorectal cancer; CAFs, cancer-associated fibroblasts.

data and the reliability of their *in vivo* behavior still needs further exploration (86-88). Exosomes derived from macrophages exhibit different functions from those of other immune cells, such as NK cells mentioned above (93,94). They can promote the occurrence and development of CRC through mechanisms such as inhibiting the Hippo signaling pathway and adsorbing miR-34a-5p (93,94).

In CRC, exosomes from tumor cells mainly arise from three types of cells: CRC cells, cancer associated fibroblasts (CAFs) and hepatocellular carcinoma (HCC), exosomes from different sources can promote the occurrence and metastasis of CRC through multiple mechanisms in synergy (117-119).

Exosomes derived from CRC cells. Studies (98,99) based on *in vitro* cell models have found that the exosome miR-934 induces polarization of M2-type macrophages by down-regulating phosphatase and tensin homolog (PTEN) expression and activating the PI3K/protein kinase B (PI3K/AKT) signaling pathway (95); miR-372-5p targets the PI3K/AKT/NF-κB pathway and regulates the expression level of programmed death-ligand 1 in CRC cells and macrophages (96). The mechanisms verified in *in vivo* mouse models include: Hemopoietic stem/progenitor cell 111 which alters the lipid metabolism of CAFs by phosphorylating ATP-citrate lyase (97); circ-SCP2 which promotes

the interaction between polypyrimidine tract binding protein 1/insulin-like growth factor 2 mRNA-binding protein 1 (PTBP1 and IGF2BP1) by regulating the miR-92a-1-5p/IGF2BP1 pathway (98); miR-188-3p which targets the PH domain and leucine-rich repeat protein phosphatase 2 and activates the AKT/mTOR pathway, thereby activating hematopoietic stem cells (99); miR-425-5p which promotes M2-like polarization of macrophages and inhibits the pro-inflammatory response of T cells (100). A disintegrin and metalloproteinase 17 targets vascular endothelial cells and enhances vascular permeability via modulating the localization of calcineurin on cell membrane (101). The mechanisms further supported by clinical sample evidence include: miR-106a-5p promotes the polarization of M2-type macrophages by inhibiting suppressor of cytokine signaling 6 and activating the JAK2/STAT3 pathway (102); heat shock protein 90 β1 promotes liver metastasis of CRC by forming polymorphonuclear neutrophils (103). miR-1825 promotes angiogenesis and liver metastasis of CRC cells by inhibiting inhibitor of growth protein 1 and activating the TGF-β/Smad2/Smad3 signaling pathway (104). In addition, the exosome miR-224-5p from CRC cells has been confirmed to promote resistance to 5-fluorouracil (5-FU) by regulating S100 calcium-binding protein A4 (S100A4), this mechanism is also supported by clinical data, further highlighting the

important role of exosomes in mediating chemotherapy resistance (105).

Exosomes derived from CAFs also carry out a key role in drug resistance and tumor progression. The mechanisms verified in *in vivo* mouse models include: Exosome miR-92a-3p which can activate the Wnt/ β -catenin pathway and block mitochondrial apoptosis by directly inhibiting F-box and WD repeat domain containing 7 and modulator of apoptosis 1, thereby inducing chemotherapy resistance in CRC cells (20). Methyltransferase-like 3 which can induce Acyl-CoA synthetase long-chain family member 3 m6A modification and stabilize its expression, promote the proliferation and metastasis of CRC, and inhibit ferroptosis (106). In addition, a study shows that circ-0067557 not only participates in drug resistance, but also promotes the occurrence, metastasis and chemical resistance of CRC through the Lin28A/Lin28B pathway (107). Conversely, a study that used *in vitro* cell models found that CAFs can also target miR-330-3p through TP53 target 1 carried out by exosomes, enhance the activity of CRC cells, promote epithelial-mesenchymal transition and inhibit apoptosis, thereby promoting tumor progression (108).

In addition, exosomes derived from HCC are also involved in regulating the progression of CRC. As demonstrated by a study using an *in vivo* mouse animal model, HCC-derived exosomes inhibit the expression of the sarcoma gene through miR-203a-3p, thereby upregulating the level of E-cadherin and ultimately promoting the occurrence and development of CRC (109).

Exosomes derived from blood exhibit a promoting effect on the development of CRC through different regulatory mechanisms. For instance, a study using *in vivo* mouse models, revealed that blood-derived exosomes promote the occurrence and progression of CRC by mediating the miR-338-3p/musashi RNA-binding protein-1 axis through circ-FMN2 (110). However, another study using only *in vitro* cell models indicated that blood-derived exosomes might regulate the miR-653/zinc finger E-box binding homeobox 2 (ZEB2) pathway through circ-0004771100 and be involved in the occurrence of 5-FU resistance (111).

Food-derived exosomes have demonstrated excellent potential to inhibit the development of CRC. For instance, a study using an *in vivo* mouse model demonstrated that exosomes derived from camel milk can reduce the expression of TNF- α and IL-6 genes in CT-26 cells (112). Exosomes derived from milk target DNA methylation transferase-1 through miR-148a to inhibit the activity of CRC activators (113). Another study using only *in vitro* cell models demonstrated that exosomes derived from buffalo milk exacerbate endoplasmic reticulum stress through miR-27b, causing the death of CRC cells (114). To the best of our knowledge, clinical evidence is still lacking regarding the role of food-derived exosomes in CRC.

Exosomes of plant origin mainly include those from Boraginaceae (comfrey) and Ranunculaceae (buttercup). Preliminary studies suggest that plant-derived exosomes may possess potential anti-tumor effects. For example, a study using *in vivo* mouse models revealed that Shikonin in exosomes derived from comfrey markedly upregulates the level of apoptotic factor BCL-2-associated X protein, promotes cancer cell

death and inhibits the progression of CRC (115). In addition, total coumarin in exosomes derived from Ranunculaceae upregulates miR-375-3p, thereby inhibiting angiogenesis in tumor cells and suppressing the occurrence and development of CRC, however, this conclusion is only based on *in vitro* cell models and still requires more *in vivo* and clinical evidence to support it (116).

5. Diagnostic and therapeutic importance of exosomes

Exosomes as notable markers for the diagnosis of CRC. Currently, clinical treatment strategies for CRC include early-stage endoscopic or surgical resection and for advanced stages, radiotherapy, chemotherapy, immunotherapy and targeted therapy (120,121). Patient survival for patients with CRC is associated with early diagnosis and treatment. However, since CRC is not easily detected in its early stages, several patients are diagnosed at advanced stages (122). Colonoscopy still remains the gold standard for the early diagnosis of CRC, however, due to its invasive nature, several patients miss the opportunity for early diagnosis. Therefore, there is an urgent need for reliable, non-invasive biomarkers capable of predicting and diagnosing CRC at an early stage. In recent years, exosomes have attracted attention as potential diagnostic tools, since they carry different molecules that reflect their origin (123-125).

Previous studies demonstrated that the expression levels of long non-coding RNAs NAMPT-AS (126) and LINC02418 (127), carried by serum exosomes, were markedly increased in patients with CRC, thus highlighting their potential as promising biomarkers for the diagnosis of CRC. In the study by Fabijanec *et al* (128), plasma exosome-derived microRNA (miR)-193a-3p was identified as a valuable biomarker for distinguishing patients with CRC from those with colorectal adenomas. In addition, the elevated levels of miR-461 (129), miR-205-5p (130), miR-6803-5p (131), miR-27a, miR-130a (132), as well as the reduced levels of miR-377-3p, miR-381-3p (133), miR-139-3p (134), miR-150-5p and miR-99b-5p (135), were associated with the initiation and progression of CRC. Notably, Wang *et al* (136) revealed that miR-125a-3p upregulation was particularly associated with the occurrence of early-stage colon cancer. Additionally, the increased levels of circular RNAs GAPVD1 (137) and PNN were also involved in CRC development (138). Furthermore, differential protein expression profiles of exosomes isolated from ascites (139) and urine (140) could serve as effective diagnostic indicators for CRC, consistent with the findings reported by Ma *et al* (141).

Exosomes serve as a potential tool for the treatment of CRC. Exosomes can carry several bioactive molecules and are involved in intercellular communication. Targeted inhibition of tumor-promoting exosome production, release or uptake can effectively regulate tumor cell proliferation, invasion and metastasis (142). Additionally, exosomes exhibit excellent biocompatibility, high stability and homing capacity, thus making them ideal nanocarriers for efficiently delivering therapeutic drugs in CRC (143). Therefore, exosomes derived from different sources hold considerable potential and value in CRC treatment.

In vitro experiments have shown that exosomes derived from CRC cells loaded with 5-FU can effectively promote apoptosis of CRC cells (125,144). Further research has shown that exosomes from various cell sources have all demonstrated good drug delivery potential in *in vivo* models. For instance, Li *et al* (145) found that exosomes of CRC cells loaded with doxorubicin have excellent tumor targeting properties. They can not only effectively inhibit tumor growth but also markedly reduce the cardiotoxicity of doxorubicin. Similarly, exosomes derived from NK cells, as delivery carriers of oxaliplatin, can enhance its anti-tumor effect and improve the prognosis of patients with CRC (91). Liu *et al* (146) research revealed that miR-128-3p delivered by exosomes carries out a key role in regulating the resistance of CRC cells to oxaliplatin, providing a new approach for reversing clinical chemotherapy resistance. In addition, exosomes derived from mesenchymal stem cells can considerably inhibit the growth of CRC cells after loading doxorubicin (147). Dendritic cell-derived exosomes coated with 5-FU can also enhance their anti-colon cancer effect (92). In the development of novel delivery systems, Wu *et al* (148) constructed an exosome-liposome hybrid nanoparticle loaded with ALKBH5 mRNA, which demonstrated a notable effect on the development of CRC in preclinical models, further expanding the application prospects of exosomes in precise drug delivery.

6. Challenges and future perspectives

The present review systematically summarizes the key molecules and mechanisms underlying the dual effects of exosomes derived from different sources on CRC, with the aim of advancing their diagnostic and therapeutic potential. By integrating current evidence, clinicians could gain a deeper understanding of the biological characteristics of exosomes, thereby providing additional strategies for the diagnosis and treatment of CRC. However, prior to their wide application in clinical practice, key challenges remain. First, the lack of technology and standards, the separation and purification techniques of exosomes still have limitations. It is difficult to efficiently obtain exosomes from specific cell sources from complex biological samples, and the existing methods face difficulties in large-scale production. More importantly, the lack of a unified standardized scheme, from separation and identification to functional analysis, may lead to poor comparability and repeatability among different research results. Second, the extreme complexity of the biological functions of exosomes. The function of exosomes is not static but highly dependent on the tumor microenvironment, disease stage and the physiological and pathological state of the body. This characteristic brings great difficulties to the precise interpretation of its function. Third, the insufficiency of evidence for clinical transformation. At present, preclinical and clinical research on the application of exosomes in the treatment of CRC is still very limited, and their *in vivo* safety, targeted delivery efficiency and long-term efficacy still need to be systematically verified.

To accelerate the translation of exosome research in clinical applications, several key steps should be considered. First, to promote technical standardization and overcome the problem of sample heterogeneity, the top priority in the future is to

establish recognized technical standards. This includes formulating standard separation operation procedures for different sample sources (such as plasma and tissue fluid) and utilizing high-resolution sorting techniques (such as immunoaffinity capture and microfluidic technology) to address the challenge of ‘sample source variability’, thereby achieving high-purity acquisition of specific exosome subpopulations. Second, deeply explore the separation and purification technology of exosomes could ensure efficient isolation and application. Third, in-depth studies should be performed to evaluate the dynamic changes and precise mechanisms of exosomes during different stages of CRC, including initiation, progression, metastasis and drug resistance. Fourth, systematic research should be conducted to identify and validate exosomal biomarkers, thus promoting standardized classification and functional analyses. Finally, preclinical and clinical trials are urgently needed to evaluate the safety and efficacy of exosome-based applications in CRC.

7. Summary

In summary, exosomes derived from different sources play pivotal roles in CRC, thus providing promising opportunities for their clinical application (149). However, their dual function on CRC progression, both promoting and repressing the development of CRC, is considerably associated with their heterogeneous origin (84,93). Therefore, a comprehensive understanding of this source-dependent functional heterogeneity is of great importance for advancing CRC therapy. Despite their notable potential, the clinical application of exosomes is hindered by notable challenges, including their complex molecular mechanisms and the lack of standardized isolation protocols. Collectively, exosomes represent a powerful tool for deepening the understanding of CRC biology and oncology, while offering novel directions and strategies for the development of innovative diagnostic and therapeutic approaches.

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Authors' contributions

ZG, HZ and QL contributed to the conception and overall design of the study. ZG and HZ drafted the manuscript and prepared the figures and tables. QL reviewed and revised the manuscript. All authors read and approved the final version of the manuscript. Data authentication was not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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