Technology in Cancer Research & Treatment
Volume 22: 1-6

DOI: 10.1177/15330338231185008
journals.sagepub.com/home/tct

The Role of Extracellular Vesicles in Colorectal Cancer

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Abstract

Extracellular vesicles (EVs) are a class of spherical vesicles that are produced by active secretion of cells and encapsulated by phospholipid bilayers. In recent years, numerous studies have shown that EVs play pivotal roles in the regulation of intercellular communication between colorectal cancer (CRC) cells and target cells, and can regulate the proliferation, metastasis, and infiltration of tumor cells by regulating the microenvironment of tumor cells. EVs carry specific molecular substances in source CRC cells and are expected to serve as new molecular markers for the detection of cancers. This review highlights the current state of research and progress of potentially incorporating EVs in the diagnosis and treatment of CRC.

Keywords

Colorectal cancer, extracellular vesicles (EVs), treatment, diagnosis

Received: September 20, 2022; Revised: April 18, 2023; Accepted: June 8, 2023.

Introduction

With average life expectancies increasing globally, malignant tumors are set to become one of the main causes of death in the global community and an important obstacle to further prolong life expectancy.[1] In 2020, there were more than 19.3 million newly diagnosed cancer patients and 10.0 million cancer deaths worldwide.[2] Colorectal cancer (CRC) ranks as one of the most diagnosed cancers, with an incidence rate of roughly 1.9 million cancer cases and 915 900 deaths worldwide.[2] Currently, CRC ranks second in cancer incidence and fourth for cancer mortality in China.[3] From 2000 to 2016, the incidence and mortality rates of CRC showed an increase year by year. Despite the adoption of various treatment strategies such as surgical resection and combined chemotherapy, there is still a lack of effective treatments in certain scenarios due to possibility of tumor recurrence and metastasis.[4] Therefore, the overall prognosis of CRC patients worldwide remains poor, especially at advanced stages.[5,6] This is further compounded by the fact that current screening tests do not have a high detection rate for early CRC. The lack of effective screens means there is an urgent need for improved screening modalities to improve the early detection rate of CRC. In recent years, liquid biopsy research on CRC biomarkers and extracellular vesicles (EVs) has undoubtedly provided a promising direction, and have now become one of the main focuses of the current CRC research field.

EVs are a class of spherical vesicles that are produced by the active secretion of cells and are encapsulated by phospholipid bilayers and range in size from nanometers to micrometers (Figure 1).[7–10] EVs are rich in proteins, lipids, and nucleic matter and participate in the exchange of materials and information between cells.[11–13] It originates from the direct budding of membrane-encased vesicles or by fusion on the surface of multivesicular body.[14,15] EVs also have different qualitative physicochemical properties and biochemical characteristics. EVs can be divided into three types based on their particle size,

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generation method, and membrane surface markers: Exosomes(50-100 nm), microvesicles (100-1000 nm), apoptotic bodies (50-500 nm), and so on.[16] Among them, exosomes are the most widely studied, followed by microvesicles.[17] In recent years, numerous studies have shown that EVs can act as transmitters of genetic information, carrying and transmitting signal molecules to adjacent and distant cells, thereby regulating the physiological and pathological states of cells.[18–25] Therefore, EVs play pivotal roles in the regulation of intercellular communication between tumors cells and target cells, and can regulate the proliferation, metastasis, and infiltration of tumor cells by regulating the microenvironment of tumor cells.[26] EVs carry specific molecular substances in the source tumor cells, and could serve as new molecular markers for the detection of cancers.[27] The lipid structure of EVs can protect the contents from being degraded, while EVs have specific receptors that provide some inherent targeting capabilities.[28–30] These advantages are conducive to the enrichment of drugs in the lesion after systemic administration, thereby reducing the drug dosage requirements and the toxic side effects of systemic administration.[30] The special structure of the spherical carrier is also a good tool for new drug development.[31,32] This review highlights the research progress of EVs in the diagnosis and treatment of CRC.

Diagnostic Application of EVs

The prognoses of CRC patients is associated with its corresponding disease stage. The 5-year survival rate of patients with early-stage CRC can reach roughly 90%, while the 5-year survival rate of patients with advanced-stage CRC is less than 20%.[33]Many patients with CRC have no obvious clinical manifestations in the early stage, leading this to be a unique problem in the field of CRC diagnosis but also allows for the incorporation of potential biomarkers in exploring treatment new treatment options. Evidence indicates that tumor cell EVs contain multiple types of RNAs with tumor specificity and can serve as potential biomarkers.[34] In previous studies, EV' miRNA found in CRC patients was linked to a CRC diagnosis. Zhang et al[35] found that the expression levels of miR-17-5p, miR-181a-5p, miR-18a-5p, and miR-18b-5p were significantly increased in CRC plasma exosomes, suggesting that these miRNAs may serve as potential noninvasive diagnostic biomarkers for CRC. Moreover, studies indicate that specific miRNAs (miR-92a-3p, miR-196b-5p, miR-146a-5p, and miR-155-5p) upregulated in malignant tissues were released and detected in the plasma, which support their potential as noninvasive diagnostic markers of CRC.[36,37] In addition to miRNAs, lncRNAs are also abundantly enriched in EVs from CRC patients, which is of significance in CRC diagnosis.[38] The serum level of EVs containing linc01836 expression was increased in cancer serum from CRC patients and declined after resection.[39] Additionally, high Linc01836 expression was associated with lymph node metastasis and histological stage.[39] At the same time, combined detection of Linc01836, Cyfra21-1, and CEA in serum used for diagnosis of CRC could potentially improve sensitivity.[39] In addition, the study showed that the expression levels of 6 serum lncRNAs (LNCV6_116109, LNCV_108266, LNCV6_98390, LNCV6_38772, LNCV6_84003 and LNCV6_98602) in CRC patients were significantly increased and had potential to be used as biomarkers for early diagnosis of CRC.[40] With the development of RNA-seq technology, scientists have identified tens of thousands of EVs containing circRNAs that can interact with miRNAs and transcription factors to regulate gene expression. EV-circRNAs are involved in various biological functions of cancer and play an important role in the occurrence and development of CRC. Thus, the serum level of EVs containing circLPAR1 and circ_PTPRA expression declined in cancer serum from CRC patients and recovered after resection.[41,42] Moreover, proteins in CRC EVs can also regulate the occurrence and progression of CRC. Zhang et al[43] found that the level of CPNE3 was significantly increased in CRC patients, especially in patients with advanced TNM or distant metastasis. Combined detection of CPNE3 and CEA in the diagnosis of CRC showed a sensitivity of 81.2% and specificity of 84.8%.[43] Furthermore, it is worth investigating whether combined detection of these effective biomarkers could further improve the diagnostics of CRC detection.

Therapeutic Application of EVs

EVs can potentially become an optimal therapy for CRC given the fact that it demonstrates promising properties concerning drug delivery, antigen presentation, and less biological barriers.[44–48] As an easy-to-use, nontoxic carrier can be produced with targeted cargo, including proteins, micromolecules as well as RNA, with comparable biological stability and can be transported without enzymatic interference or phagocytosis.[49,50]

Certain experiments have shown the potential role of EVs in CRC. EVs loaded with miR-379 inhibited proliferation and spread of colorectal tumor cells.[51] Other investigations showed that EVs demonstrated a pro-angiogenesis role in CRC via miR-221-3p pathway, and showed a novel diagnostic power with a signature of four miRNAs, including miR-19a-3p, miR-203-3p, miR-221-3p, and let-7f-5p.[52] As an optimal chemotherapy encapsulation candidate, EVs not only reduce possible side effects but may also boost therapeutic efficiency. To reduce the severe side effects of chemotherapeutic drugs on vital organs, encapsulation of chemotherapeutic molecules in nanocarriers is a reasonable solution to reduce the risk of their side effects and improve therapeutic efficiency. Recently, researchers bioengineered a doxorubicin-loaded AS1411 aptamer exosome to target CRC cells.[53] Drug delivery can be a remarkable tool and could represent a massive achievement in both safety and efficiency for various therapies. Examples of improved performance were seen, for example, in the chemotherapeutic performance of oxaliplatin which demonstrated that it could be enhanced by EVs-delivered miR-1915-3p.[54] Meanwhile,

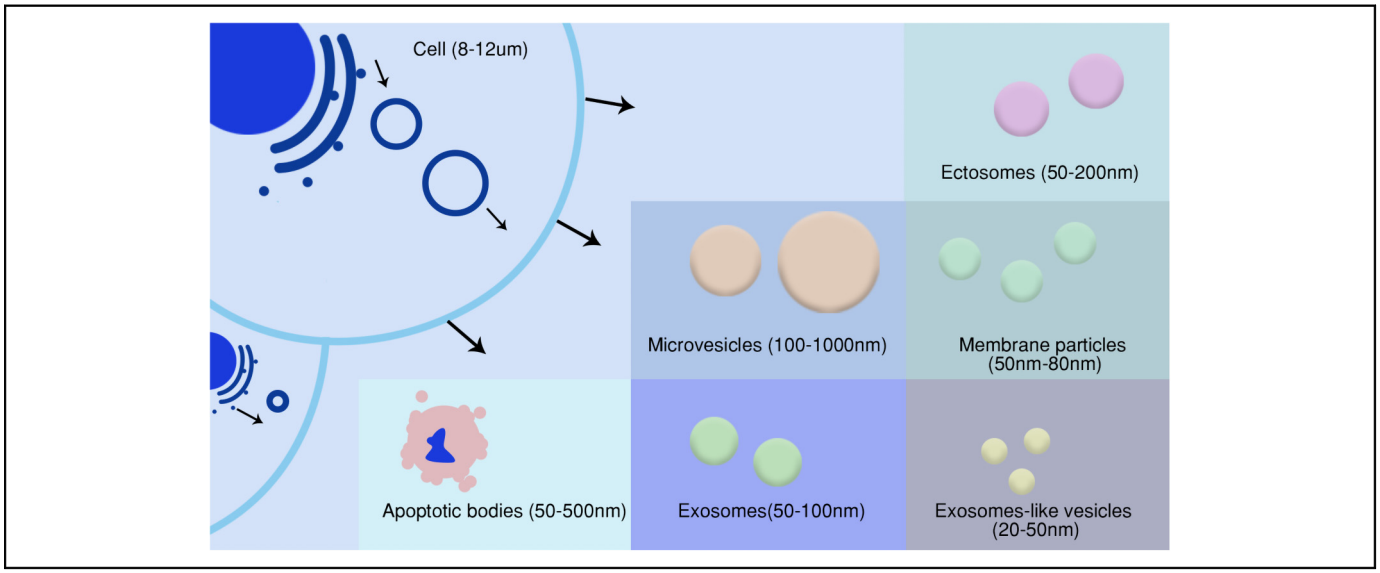

Figure 1. Illustration of different sizes in cell, apoptotic bodies, microvesicles, ectosomes, membrane particles, exosomes-like vesicles, and exosomes.

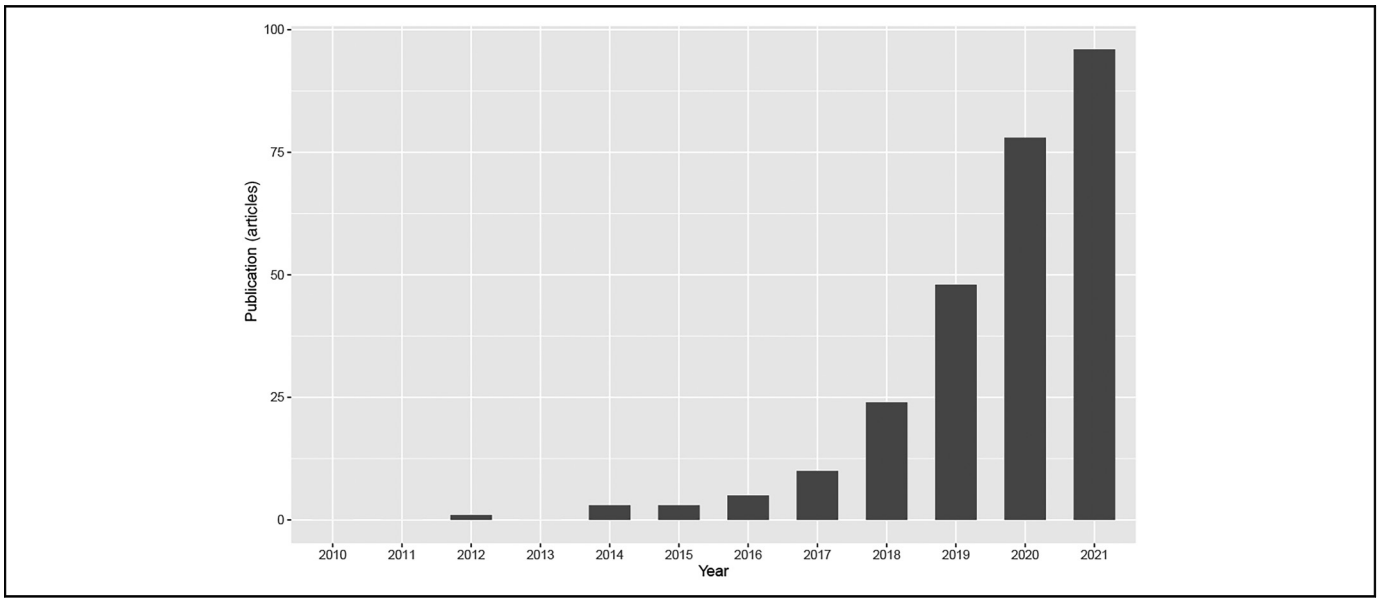

Figure 2. Publications of EVs and bioinformatics retrieved from PubMed from 2010 to 2021.

a circulating exosome miRNA signature (miR-6087/miR-132-5p/miR-93-3p/miR-320d) has been identified to have adjuvant chemotherapeutic benefits.[55] Chemosensitivity of CRC can also be impacted by exosomes, as CircPTEN derived from exosome enhanced chemosensitivity by modulating glycolysis via miR-766-5p/TRIM67.[56]

On the other hand, delivery by EVs may also promote disease progression of CRC as well. For instance, EVs-delivered miRNA-25 targeted SIRT6 inhibition and further enhanced the tumor progression via the Lin28b/NRP-1 axis in CRC.[57] Another study indicated that EVs derived from cancer-associated fibroblasts with lncRNA SNHG3 could facilitate tumor proliferation by activating the miR-34b-5p/HuR/HOXC6 signaling pathway.[58]

Immunotherapy is increasingly essential in treatment managements for CRC, aiming to suppress metastatic tumor cells and disease progression via remodeling the immune system.[59] Cancer vaccines are some of the most promising applications. EVs with heat shock protein and major histocompatibility complex-1 derived from tumor cells demonstrate a unique CEA-specific antitumor response.[60] Another recent study showed that miR-124-3p enriched tumor-derived EVs exerted a significant antitumor immune activity in a CT-26 induced in vivo model.[61] Interestingly, immunotherapeutic responses could be correlated to EVs-based m^6A regulator gene methylation modification pattern in colon cancer.[62] A m^6A-related exosome gene score can be developed to characterize potential immune phenotypes and diverse immunotherapy strategies.[62]

Table 1. Summary of Clinical Trials Relating to Extracellular Vesicles (EV)/Exosomes/Microparticle Registered on the ClinicalTrial.gov.

ClinicalTrial.gov Identifier	Study official title	Number of patients	Study type	Responsible party
NCT04523389	Contents of circulating extracellular vesicles: Biomarkers in CRC Patients	172	Observational	Centre Hospitalier Universitaire Dijon
NCT04394572	Identification of New Diagnostic Protein Markers for Colorectal Cancer (EXOSCOL01)	80	Observational	Centre Hospitalier Universitaire de Reims.
NCT05375604	A Study of exoASO-STAT6 (CDK-004) in Patients With Advanced Hepatocellular Carcinoma (HCC) and Patients With Liver Metastases From Primary Gastric Cancer and Colorectal Cancer (CRC)	30	Interventional (clinical trial)	Codiak BioSciences
NCT04298398	Impact of Group Psychological Interventions on Extracellular Vesicles in People Who Had Cancer (MindGAP-P)	108	Interventional (clinical trial)	Instituto Portugues de Oncologia, Francisco Gentil, Porto
NCT02694562	Microparticle Enhanced Cytotoxic Transarterial Embolization Therapy (MIRACLEIII)	18	Interventional (clinical trial)	Boston Scientific Corporation
NCT03969784	Microparticles in Peritoneal Carcinomatosis of Colorectal Origin	40	Interventional (clinical trial)	Assistance Publique Hopitaux De Marseille

Perspective

It is important to remember that the increased focus on novel techniques of bioinformatics will also increase the knowledge base of EVs. It has greatly contributed to the thriving advances in both basic and clinical investigations. During the last ten years, there has been a substantial increase in publications dealing with the field of exosome and bioinformatics (Figure 2). This includes potential diagnostic biomarkers, mutation features, and translational assessments of first-line therapies, along with clinical trials, which could be benefits from bioinformatic contributions. Clinical investigations, either focusing on the biomarker or therapeutic values of exosomes, have been registered. Numerous ongoing clinical trials relating to EVs and CRC in ClinicalTrial.gov have been summarized (Table 1). In other words, EVs-based biomarkers, and novel therapies are set to become some of the most innovative contributors in clinical practices in the near future.

Conclusion

EVs have shown tremendous bench-to-bed potential with excellent properties relating to cellular sensitivity, specificity, and pharmaceutical stability. Although it remains difficult for standardized processing, EVs have the potential to be influential and widely used given their remarkable potential. A variety of applications, RNAs/proteins/drugs, or other molecules, makes EVs an ideal carrier for both chemotherapy and immunized treatment in CRC. Future investigation of EVs will be improved by bioinformatics and lead to more focused methods for optimization, purification, functional characterization, and ideally, better in vivo results.

Authors contributions

Yousheng Li, Yujian Xia, Chaoran Yu, and Johann Helwig Ernest conceived and revised the ideal of the study. Yousheng Li, Yujian Xia, Chaoran Yu, and Johann Helwig Ernest wrote the paper. Yousheng Li, Yujian Xia, Chaoran Yu, and Johann Helwig Ernest revised the final manuscript. All authors discussed the results and approved the final manuscript.

Availability of Data and Materials

The datasets supporting the conclusion of this article are included within the article.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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