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REVIEW

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Small extracellular vesicles promote the formation of the pre-metastatic niche through multiple mechanisms in colorectal cancer

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ABSTRACT

Colorectal cancer (CRC) ranks among the most prevalent global malignancies, posing significant threats to human life and health due to its high recurrence and metastatic potential. Small extracellular vesicles (sEVs) released by CRC play a pivotal role in the formation of the pre-metastatic niche (PMN) through various mechanisms, preparing the groundwork for accelerated metastatic invasion. This review systematically describes how sEVs promote CRC metastasis by upregulating inflammatory factors, promoting immunosuppression, enhancing angiogenesis and vascular permeability, promoting lymphangiogenesis and lymphatic network remodeling, determining organophilicity, promoting stromal cell activation and remodeling and inducing the epithelial-to-mesenchymal transition (EMT). Furthermore, we explore potential mechanisms by which sEVs contribute to PMN formation in CRC and propose novel insights for CRC diagnosis, treatment, and prognosis.

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Introduction

Colorectal cancer (CRC), a gastrointestinal malignancy, poses a serious threat to human life and health. Globally, it accounts for approximately 9.3 million new cases annually, ranking third among newly diagnosed tumors, constituting 10.0% of all cases. Additionally, CRC stands as most fatal cancer worldwide, contributing to 9.4% of cancer-related deaths [1]. While the 5-year survival rate s reach up to 91% for localized cases in the early stage and 73% for regional instances, most diagnoses occur at intermediate to advanced stages due to limitations in early detection and screening. Consequently, patients with CRC, particularly those with distant metastases, face a dismal 5-year survival rate of merely 14% [2]. Metastasis is the process where in tumor cells spread from the primary site to distant tissues and organs through lymphatic and blood channels for proliferation. The liver is the most common site of metastasis in colorectal cancer. Approximately 20–30% of CRC patients with CRC present with liver metastases at initial diagnosis, with progression reported in 50–60% of cases over the course of the disease [3]. Furthermore, metastases in locations such as the lung, peritoneum, nervous system, and bones are prevalent [4]. Metastasis of colorectal cancer is an organ-selective and multistep complex process that severely impacts patient health and life expectancy. Therefore, understanding the mechanism behind CRC metastasis and identifying related biomarkers for early diagnosis and treatment is critical for improving patient survival and quality of life.

The pre-metastatic niche (PMN) is defined as the supportive and receptive tissue microenvironment. It involves a series of molecular and cellular changes that form the locus of metastasis, or the fertile "soil" that prepares the "seeds" of metastatic tumor cells for colonization, thus supporting tumor settlement in distant organs and promoting tumor metastasis. In other words, PMN is the microenvironment facilitating the settlement of metastatic tumor cells in distant organs [5,6]. In 1889, Paget proposed the "seed and soil" hypothesis that states the success of metastatic cancer cell growth is largely dependent on the target organ (the soil) and the cancer cells (the seed), while emphasizing the

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importance of the microenvironment's role in metastatic success and highlighting the organotropic nature of metastasis [7,8]. Recently, numerous studies have focused on the importance of the PMN. Cao et al. reported first summatized six characteristics of the premetatatic niche, namely inflammation, immunosuppression, angiogenesis, and vascular permeability, lymphangiogenesis, organotropism, and reprogramming that promote the metastasis and localization of tumor cells [9]

Extracellular vesicles (EV) are defined as submicron-sized lipid bilayer-enclosed vesicles released by cells. Meanwhile, small extracellular vesicles (sEVs), with a diameter of 30–150 nm, are a specific subset of EVs [10]. EG Trams et al. first identified sEVs in sheep reticulocytes in 1981, and 6 y later these were termed by Johnstone as sEVs [11]. Furthermore, sEVs originate from endosomal-derived intraluminal vesicles (ILVs) and function by fusing with the intracellular side of the plasma membrane via multivesicular endosomes or multivesicular bodies (MVBs), resulting in its release into the extracellular environment [12]. Notably, the majority of cells secrete EVs, which serve as mediators of intercellular transmission of information and participate in cellular physiological and pathological processes [13]. sEVs comprise a lipid bilayer structure with typical biomolecules such as DNA, RNA, glycans, lipids, proteins, and metabolites [14]. Moreover, sEVs can transport contents to the microenvironment of tumor growth, thus promoting tumor cell growth and metastasis [15]. Numerous studies have demonstrated their involvement in tumor development and metastasis promotion by transporting various biomolecules to the tumor microenvironment. For example, miR-27a, miR130a, and miR-7641 expressions were increased in sEVs isolated from CRC patients' plasma and CRC cells [16,17]. And sEVs-mediated miR-105 from metastatic breast cancer cells induces metastasis to distant organs by downregulating and targeting the tight junction protein zonula occludens-1(ZO-1) and disrupting the barrier function of the endothelial monolayer [18]. Interestingly, the molecular and functional characteristics of sEVs evolve as the cancer progresses. Therefore, tumor-derived small extracellular vesicles (TDsEVs) have the potential to provide valuable real-time information, as well as reflect the dynamic changes in cancer progression. Given their unique molecular profile and functional characteristics that influence the formation and development of PMNs, TDsEVs have been widely recognized as a useful diagnostic and predictive biomarker [12]. It has been reported that tumor-derived sEVs have an important influence on the formation and development of the PMN [6,19]. They regulate intercellular communication between tumor cells and normal mesenchyme, tumor-associated fibroblasts, and local immune cells in the tumor microenvironment [20], promoting angiogenesis, etc., to promote tumor growth and invasion. Over time, many studies have continued to confirm the various molecules that regulate PMN's progression, highlighting the molecular and cellular changes in the PMN that support future metastatic tumor growth. It has been proposed that PMN is the result of an integrated systemic effect of tumor secretory factors and tumor extracellular vesicles, with EVs contributing to the time sequence of events during PMN evolution [21].

To elucidate the role played by sEVs in CRC's PMN, we systematically reviewed existing literature through the following five steps, which are based on Danielle et al.'s methodology. 1) Identify a research question: we pose a research question, how do EVs in CRC contribute to PMN formation?; (2) identify relevant studies: We selected several PMN characteristics such as inflammatory factors, promoting immunosuppression, increasing angiogenesis and vascular permeability, promoting lymphangiogenesis and lymphatic network remodelling, determining organophilicity, promoting stromal cell activation and remodelling and promoting the epithelial-to-mesenchymal transition as the scope of our study; (3) select relevant studies: we screened suitable literature by searching electronic databases and major journals, optimising inclusion and exclusion criteria; (4) chart data from these studies: data obtained was organized, with charts and graphs plotted for better data visualisation (Figure 1); and (5) collate, summarize and report the results [22]. Thus, through this review, we aim to unravel the mechanisms of sEVs influencing the PMN and offer insights into

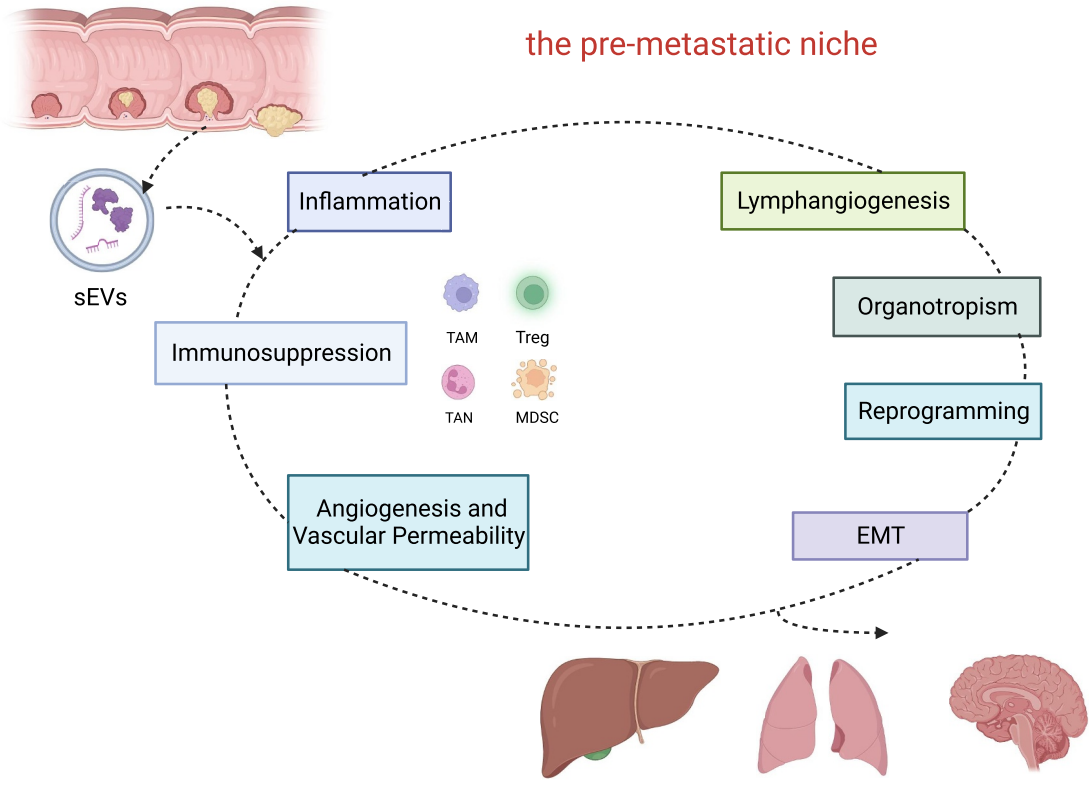

Figure 1. The role of sEVs derived from CRC in the formation of pre-metastatic niche.

the diagnosis, treatment, and prognosis of CRC metastasis.

Small extracellular vesicles promote the upregulation of inflammatory factors in the pre-metastatic niche of colorectal cancer

Tissue damage by some infectious, chemical, or mechanical factors triggers a chronic immune response that leads to cell proliferation and regeneration. If the resulting immune response does not completely resolve the damage, the microenvironment rich in inflammatory factors maintains a proliferative state in an attempt to repair triggers, leading to the accumulation of genetic errors and abnormal proliferation [23]. This chronic inflammation drives tumor development and metastasis, constituting a crucial factor in PMN formation. One of the important mechanisms in the development of colorectal cancer is the interaction between tumor cells and their microenvironment. This proto-oncogenic microenvironment comprises inflammatory and immune cells, including macrophages and neutrophils, cancer-associated fibroblasts (CAF), some environmental conditions such as hypoxia, soluble factors, signaling molecules, and extracellular matrix (ECM) components. Tumor-derived secretory factors (TDSFs) are released by the primary tumors including pro-angiogenic factors (e.g. vascular endothelial growth factor (VEGF)) and pro-inflammatory factors (e.g. tumor necrosis factor alpha (TNFα), transforming growth factor beta (TGF-β), interleukins (ILs)), prepare distant niched by recruiting myeloid cells in a paracrine manner to future pre-metastatic niche-forming sites [24].

Yan et al. found that the extracellular vesicle miR-6803-5p, induced by lipopolysaccharide (LPS), enhances the expression of metastatic bioactive molecules IL-6 and TNF-α in CRC cells and ultimately mediates intercellular communication [25].

Table 1. sEvs promote upregulation of inflammatory factors in the pre-metastatic niche of colorectal cancer.

Characteristic	sEVs cargos	Tissues and/or cells	Mechanism and function	Refs
Inflammation	miR-6803-5p	HCT116	Promotes cancer cell proliferation and invasion through the PTPRO/NF-κB axis in colorectal cancer and enhances inflammation	25
Inflammation	ITGBL1	HCT116′Caco2, LoVo, SW480, SW620; plasma from CRLM; CRC tissues	Stimulation of TNFAIP3-mediated NF-κB signaling pathway activates fibroblasts, and activated fibroblasts secrete pro-inflammatory cytokines	27
Inflammation	microRNA-21-5p (miR-21)	SW480, SW620; plasma;CRC tissues	Polarization of hepatic macrophages to an interleukin il –6 producing phenotype via TLR7 induces the formation of an inflammatory microenvironment	28
Inflammation	integrins	HT29	Up-regulation of pro-inflammatory S100 molecule expression in the distal tissue microenvironment	29

Notably, apoptotic exosome-like vesicles (AEVs) may be key inflammatory mediators. For example, AEVs containing sphingosine 1-phosphate receptor (S1PR1) induce macrophages to secrete pro-inflammatory cytokines and activate nuclear factor kappa-B (NF-κB) and p38 mitogen-activated protein kinase (MAPK), thereby promoting cellular inflammation, cancer, and apoptosis [26]. Another study by Ji et al. found that CRC-derived integrin beta-like 1 (ITGBL1)-rich sEVs stimulate the tumor necrosis factor alpha-induced protein 3 (TNFAIP3)-mediated NF-κB signaling pathway to activate fibroblasts, which in turn induce PMN formation and promote metastasis by secreting pro-inflammatory cytokines (e.g. IL-6 and IL-8) [27]. Colorectal cancer-derived sEVs with high expression of microRNA-21-5p (miR-21) expressions polarize hepatic macrophages to an interleukin IL-6 producing phenotype via toll-like receptor 7 (TLR7), inducing the formation of an inflammatory microenvironment and promoting liver metastasis in CRC [28]. Host stromal cells in the PMN may upregulate the expression of inflammatory factors in response to stimulation by TDsEVs. Hoshino et al. reported that integrins secreted by sEVs upregulated the expression of pro-inflammatory S100 molecules in the distal tissue microenvironment [29]. Additionally, sEVs can transport inflammatory factors to the bloodstream, reaching the PMN and fostering a tumor-favorable inflammatory microenvironment. Table 1 details the examples used in this section.

Small extracellular vesicles promote immunosuppression in pre-metastatic niche of colorectal cancer

The immune system serves as a critical defense against cancer metastasis. The presence of immune surveillance makes it possible for each step of tumor development to be detected by the body and thus foreclosed, especially the complex process of distant metastasis. Immune cells such as $CD8^+$T cells, natural killer (NK) cells and monocytes help prevent tumor metastasis without affecting the growth of the primary tumor [30]. Several studies indicate that sEVs exert

Table 2. sEvs promote immunosuppression in pre-metastatic niche of colorectal cancer.

Characteristic	immune cell	sEVs cargos	Tissues and/or cells	Mechanism and function	Refs
Immunosuppression	TAM	miRNAs (miR-25-3p,miR-130b-3p,miR-425-5p)	HCT116′SW620	activation of PI3K/Akt signaling pathway regulates PTEN, induces M2 polarization in macrophages, enhances EMT and secretion of VEGF.	37
Immunosuppression	TAM	miR-145	DLD-1	the downregulation of *histone deacetylase 11* 'polarized macrophage-like cells into the M2-like phenotype	38
Immunosuppression	TAM	miR-203	plasma	Induce macrophage M2 polarization to promote the formation of PMN	39
Immunosuppression	TAM	miR-934	HCT-8′LoVo′HT-29′Caco-2; plasma; CRC tissues	Downregulation of PTEN expression and activation of PI3K/AKT signaling pathway induce M2 macrophage polarization, and secretion of CXCL13 promotes the formation of PMN	40
Immunosuppression	TAM	lncRNA RPPH1	HCT8′SW620′HT29; CRC tissues	RPPH1 induces EMT in CRC cells by interacting with TUBB3; CRC cell-derived exosomes translocate RPPH1 into macrophages and mediate macrophage M2 polarization	41
Immunosuppression	TAM	miR-106	Plasma;HCT116 (EMT-CRC)	Activation of PI3Kγ/AKT/mTOR signaling pathway to promote the polarization of M2 macrophages	42
Immunosuppression	TAM	miR-1246	HCT116′DLD-1′HT29′H358	Colon cancer cells with GOF mutp53 promote the formation of unique reprogrammed macrophage populations by releasing miR-1246-containing exosomes	44
Immunosuppression	TAM	lncRNAs	HT29($BRAF^{V600E}$ mutant';CRC tissues	Promotes macrophage polarization to the M2 subtype and enhances the secretory function of macrophages and fibroblasts, and induces the formation of an immunosuppressive microenvironment	47
Immunosuppression	TAM	tRF-3022b	CRC tissues; Plasma	Reduced M2 macrophage polarization by binding to LGALS1and MIF	48
Immunosuppression	TAM	miR-1827	human umbilical cord mesenchymal stem cells	Down-regulation of SUCNR1 expression inhibits M2 macrophage polarization	49
Immunosuppression	TAM	CCL2	MC38 cell	Activated macrophage recruitment and shifted the M1/M2 paradigm to a M2 phenotype	50
Immunosuppression	TAM	miR-155-5p	M2 macrophages	Downregulation of ZC3H12B increases IL-6 expression in the ground to promote immune escape in colon cancer	51
Immunosuppression	TAN	circPACRGL	HCT116′SW480	Promotes neutrophil N2 polarization via miR-142-3p/miR-506-3p-TGF-β1 axis, leading to immune escape of tumors	56
Immunosuppression	TAN	mutant KRAS	DKs-8 (WT allele), DKO-1 (KRAS mutant)	Increases IL-8 production, promotes neutrophil recruitment and NET formation, and promotes metastatic and invasive capabilities	58
Immunosuppression	TAN	has-miR-4780′has-miR-3938	CRC tissues	Promotes neutrophil N2 polarization, regulates both TUSC1 and ZNF197 genes, and affects CRC invasion and metastasis	59
Immunosuppression	Treg	TGF-β1	DLD-1′WiDr	CRC-EVs induced phenotypic alteration of the T cells to Treg-like cells through activating TGF-β/Smad signaling and inactivating SAPK signaling.	65
Immunosuppression	Treg	miR-208b	SW480;SW480-OXA;NCM460; CT26	Targeting PDCD4 promotes Treg amplification, thereby promoting immunosuppression	66
Immunosuppression	MDSC	S100A9	G-MDSCs	Hypoxia upregulates HIF-1α to promote the production of sEVs by G-MDSCs, and MDSC-sEVs exacerbate the stemness of colorectal cancer cells by releasing S100A9	77

a significant role in immunosuppression during CRC metastasis [31–33].

Post-upregulation of pro-inflammatory factor expression by sEVs, the resultant local inflammatory microenvironment triggers chemokine and cytokine production by tumor cells. These factors synergize with sEVs produced by tumor cells to recruit tumor-associated macrophages (TAM), tumor-associated neutrophils (TAN), regulatory T (Treg) cells, and myeloid-derived suppressor cells (MDSC) to distant secondary sites [9]. These immune cells can suppress anti-tumor immune responses [34], aiding in the modulation of the PMN. Here, we have selected four cell types, TAM, TAN, Treg, and MDSC, to illustrate the immunomodulatory role (Table 2).

Tam

Macrophages, as the most abundant immune-associated stromal cells in the tumor environment, demonstrate diverse phenotypes in response to different stimuli. For instance, it can polarize into classically activated M2 macrophages or replace activated M2 macrophages through different stimuli in the microenvironment [35]. TAM, characterized as "M2-like", are the major myeloid subpopulation in the TME and various foster pro-tumor activities, including pro-invasion, immunosuppression and angiogenesis, which are important factors in promoting tumor progression [36]. Wang's group delineates that upon activation of CXCL12/CXCR4 axis, CRC cells secrete highly expressed miRNAs (miR-25-3p, miR-130b-3p, miR-425-5p).These miRNAs are delivered to TAMs via sEVs, and the specific mechanism involved may be to regulate PTEN through activation of PI3K/Akt signaling pathway, induce macrophage M2 polarization, enhance EMT and VEGF secretion, thereby promoting tumor metastasis [37]. Similarly, Shinohara et al. found that reported that sEV-contained miR-145 from CRC cells facilitates M2-like polarization in macrophages, advancing tumor progression [38]. Circulating tumor-derived miR-203^{+}sEVs drive distant metastasis by inducing M2-TAMs in CRC and refining PMN [39]. Zhao et al. demonstrated that CRC cell-derived miR-934^{+}sEVs induce M2 macrophage polarization through PTEN downregulation and PI3K/AKT signaling pathway activation, thereby inducing pre-metastatic ecotone formation and promoting liver metastasis in CRC by secreting CXCL13 [40]. Furthermore, Liang's group sequenced seven pairs of CRC liver metastasis specimens with surrounding normal tissues and selected the transcript with the highest abundance of lncRNA RPPH, revealing that CRC cell-derived sEVs translocate RPPH1 into macrophages and mediate macrophage M2 polarization, thereby promoting CRC metastasis and proliferation [41]. Similarly, Yang et al. demonstrated that IL-6 treatment induced CRC cells to exhibit an EMT phenotype, with the EMT- CRC-derived miR-106b^{+}sEVs promoting M2 macrophage polarization by activating the PI3Kγ/AKT/mTOR signaling pathway, resulting in CRC cell migration, invasion and EMT in vitro and liver and lung metastasis in vivo [42]. TP53 mutants (mutp53) are involved in the development of most cancers. Unlike the tumor suppressor function of the wild-type protein, mutp53 is endowed with a unique set of missense mutations resulting in a novel oncogenic activity called gain-of-function (GOF) [43]. The study by Cooks et al. demonstrated that that colon cancer cells carrying GOF mutp53 selectively shed miR-1246-rich sEVs and reprogram macrophages into a tumor-supporting and anti-inflammatory state, fueling cancer progression and metastasis [44]. The BRAF V600E mutation is a point mutation (T mutation to A) in exon 15 at nucleotide 1799, resulting in a change in the encoded amino acid 600, with valine being replaced with glutamate (V600E)'accounting for approximately 10% all patients with metastatic colorectal cancer (mCRC) [45]. Long non-coding RNAs (lncRNAs) are non-coding transcripts longer than 200 nucleotides, and they play an important role in many biological and pathological processes [46]. Zhi et al. found that CRC cells with BRAF V600E mutation can induce the formation of an immunosuppressive microenvironment by releasing sEVs containing lncRNAs that promote macrophage M2 polarization. The BRAF V600E mutation also promotes more angiogenesis and lymphatic angiogenesis in the microenvironment, thus laying the foundation for colorectal cancer metastasis [47]. In another study, Lu et al. unveiled the expression pattern of tRNA-

derived fragments (tRF) in the sEVs of tissue and plasma, identifying tRF-3022b as a potential effector of CRC tumor growth as a potential effector of M2 macrophage polarization through the binding of sEVs to galectin 1 (LGALS1) and macrophage migration inhibitory factor (MIF) [48]. Similarly, Chen's team found that human umbilical cord mesenchymal stem cells secreted miR-1827-rich sEVs, which inhibited M2 macrophage polarization by downregulating succinate receptor 1 (SUCNR1) expression, thereby reducing the proliferative, migratiory, and invasive properties of CRC cells and also blocking CRC liver metastasis in vivo [49]. Furthermore, Chen et al. showed that Da Huang Zhi Chong Wan, a Traditional Chinese Medicine, inhibits CRC liver metastasis by improving $CCL2^{+}$sEVs-mediated macrophage infiltration in mouse liver and attenuating M2 polarization, thereby PMN formation [50]. Interestingly, M2-polarized macrophages release sEVs that influence immunosuppression and immune escape in CRC, exemplified by Ma's group that M2 macrophage-derived miR-155-$5p^{+}$sEVs enhancing immune escape in colon cancer via increasing IL-6 expression through the downregulation of ZC3H12B, thus promoting CRC development and progression [51].

Tan

TANs exert varied roles, secreting proteases, reactive oxygen species, and cytokines pivotal in tumorigenesis, progression, angiogenesis, and immune regulation [52]. Similar to macrophages, TAN can be further divided into two subtypes, N1 TAN and N2 TAN. N1 TANs exhibit anti-tumor properties, whereas N2 TANs promote tumorigenesis, progression and metastasis [53]. Qi's et al. reported that that breast cancer cells enable neutrophil recruitment and N2 transformation through sEVs, thereby promoting the immunosuppression of the PMN in the lung and enabling cancer progression [54]. Similar N2 polarization mechanisms have also been reported in gastric cancer [55]. Furthermore, Shang's group found that CRC-derived sEVs carrying circPACRGL regulate miR-142-3p/miR-506-3p-TGF-β1 axis, triggering N2 polarization, promoting tumor immune escape, and advancing metastasis [56]. KRAS proteins are small G proteins that regulate membrane signal transduction and cell proliferation [57]. Shang's group found that CRC cells transfer mutant KRAS to neutrophils via sEVs and increase IL-8 secretion, promoting neutrophil recruitment and formation of Neutrophil extracellular trap (NET), which ultimately leads to CRC progression [58]. Additionally, Wang et al. unveiled that TGF-β1-induced N2 neutrophils, with the assistance of sEV-encapsulated miRNAs, potentially regulate genes such as TUSC1 and ZNF197, involved in CRC invasive metastasis, thus laying a theoretical foundation for the mechanism of invasive metastasis of CRC cells [59].

Treg

Regulatory T cells (Tregs), recognized for their immunosuppressive activity, are a heterogeneous population of T lymphocytes that significantly impact immune homeostasis [60]. In many malignancies, patients have increased levels of Tregs in their peripheral blood or tumor microenvironment, which is indicative of tumor immune tolerance and poor prognosis [61]. Wang's team showed that TDsEVs contribute to the establishment of immunologically tolerant PMN in the lung by activating Tregs [62]. Similarly, the involvement of sEVs in immunomodulatory effects related to Tregs has also been reported in other cancers [63,64]. CRC cell-derived sEVs inhibit T cell proliferation by disrupting intracellular signals, such as MAPK, AKT, and TGF-β/Smad, inducing T cell phenotypic shifts, fostering immunosuppression, and supporting tumor growth. Yamada et al. found that CRC-derived sEVs induced a phenotypic shift of T cells to Treg-like cells by activating the TGF-β/Smad signaling pathway and inactivating the SAPK signaling pathway, consequently promoting immunosuppression and advancing the PMN formations [65]. Meanwhile, Ning's group suggested that miR-208b-containing sEVs secreted by CRC have also been speculated to be conditional factor in the conversion of CD4 T cells into Tregs, promoting Treg expansion by directly targeting PDCD4, resulting in immunosuppression promotion and tumor progression. Additionally, the potential role of miR-208b as a predictive

Table 3. sEvs increase angiogenesis and vascular permeability in the pre-metastatic niche of colorectal cancer.

Characteristic	sEVs cargos	Tissues and/or cells	Mechanism and function	Refs
Angiogenesis and Vascular Permeability	miR-92a-3p	DLD-1'WiDr'COLO201'SW480	Reducing Dickkopf-3 and Claudin-11 expression in HUVECs induces partial endothelial-to- mesenchymal transition in endothelial cells, thereby promoting angiogenesis	82
Angiogenesis and Vascular Permeability	miR-25-3p	NCM460'SW480'LS174T'SW620'LOVO'HCT116	Disrupts the integrity of the endothelial barrier and induces angiogenesis, thereby promoting hepatopulmonary metastasis of CRC	83
Angiogenesis and Vascular Permeability	microRNA-135b-5p	LoVo'HT29	Inhibition of thioredoxin-interacting proteins promotes colorectal cancer cell growth and angiogenesis	84
Angiogenesis and Vascular Permeability	miR-1229	plasma; CRC tissues	Targeting HIPK2 promotes angiogenesis, thereby facilitating the formation of pre-metastatic ecotone	85
Angiogenesis and Vascular Permeability	Wnt4	HT29	Mediating β-catenin pathway conduction promotes angiogenesis in endothelial cells	86
Angiogenesis and Vascular Permeability	miR-21-5p	Lovo;SW620;HT29;SW480;HCT116;LS174T; plasma;CRC tissues	Targeting KRIT1 activates the β-linked protein signaling pathway, thereby inducing angiogenesis and vascular permeability	87
Angiogenesis and Vascular Permeability	miR-183-5p	FHC;DLD-1;HT29;HCT116;HMEC-1;NCI-H508	Targeting FOXO1 enhances angiogenesis in microvascular endothelial cells	88
Angiogenesis and Vascular Permeability	lncRNA-APC1	HCT116, DLD-1, SW480, LOVO, SW1116 and CRC tissues	Exosomes from CRC cells with lncRNA-APC1 silencing promote angiogenesis by activating the MAPK pathway in endothelial cells	89
Angiogenesis and Vascular Permeability	circTUBGCP4	HCT116;SW480 and plasma	Inhibition of miR-146b-3p promotes tip cell formation and activates the Akt signaling pathway to promote angiogenesis	90
Angiogenesis and Vascular Permeability	ANGPTL1	CRC tissues	Inhibition of JAK2-STAT3 signaling pathway, reprogramming of Kupffer cells and reduction of MMP9 expression to block vascular leakage in hepatic PMN, thereby attenuating CRC liver metastasis	91

biomarker for oxaliplatin-based chemosensitivity has also been reported [66]. Furthermore, TDsEVs carry inhibitory molecules such as cytotoxic T lymphocyte-associated protein 4 (CTLA-4) or programmed death ligand 1 (PD-L1), which promote T cell apoptosis and inhibit T cell activation and proliferation, exacerbating immunosuppression in CRC [67–69]. Moreover, this immune tolerance state can be further enhanced by recruiting immunosuppressive lymphoid and bone marrow subpopulations (MDSC and Treg) to the liver.

Mdsc

MDSC, a heterogeneous immature myeloid population that includes macrophages, granulocytes, neutrophils, and dendritic cells, play a pivotal role in immunosuppression and tumor progression by suppressing T lymphocytes and NK cells. However, after tumor initiation, the bone marrow overproduces MDSCs, which accumulate within the tumor stroma and consequently promote immunosuppression and immune escape [70]. Moreover, during tumor progression, they accumulate in the circulatory system and are recruited to the peripheral lymphoid organs and tumor sites through growth factors released by tumor cells [71]. They also play a significant role in immunosuppression, vascular permeability, and collagen remodeling, which are essential for PMN formation [72]. MDSCs have been demonstrated to mediate an immunosuppressive environment, wherein hypoxia promotes the secretion of TDsEVs. Breast cancer-derived TDsEVs containing miR-9 and miR-181a target suppressor of cytokine signaling 3 (SOCS3) and protein inhibitor of activated STAT 3PIAS3) molecules and resultantly activate the JAK/STAT signaling pathway, thereby affecting the differentiation and activation of MDSCs and enhancing their immunosuppressive effects [73,74]. Guo's et al. demonstrated that Hypoxia-induced glioma cells can stimulate the differentiation of functional MDSCs by transferring miR-29a and miR-92a to MDSCs via sEVs, thereby promoting the formation of an immunosuppressive microenvironment in tumors [75]. Furthermore, S100A8/A9, released via MDSC-derived sEVs, contribute to metastasis, angiogenesis, and immunosuppression, facilitating the establishment of the PMN in CRC and lung cancer [76]. A study on colorectal cancer by Wang's team showed that hypoxia promotes sEVs production by granulocyte MDSCs (G-MDSCs) through HIF-1α upregulation. Accordingly, MDSC-sEVs exacerbate the stemness of CRC cells through the release of S100A9, through the release of [77]. Tumor necrosis factor receptor 2 (TNFR2) facilitated MDSC-mediated immunosuppression and liver metastasis, and Ham et al. proposed that using TNFR2 inhibitors as potential strategies to hinder metastasis in various cancers, including CRC [78]. However, the relationship between the role of MDSC and sEVs warrants further investigation.

Notably, immune cells interact with each other, transforming each other and synergizing immune regulation. For example, Tian' team found that Tregs convert to "macrophage-like" cells, whereas colon cancer-derived sEVs promote tumorigenesis through miRNAs via Interferon regulatory factor 4 (IRF4) downregulation. Furthermore, IRF4 overexpression promotes Tregs transdifferentiation into macrophage-like cells (especially M1 macrophages), while Tregs downregulation weakens the anti-tumor immunosuppressive effect, thereby synergistically inhibiting the proliferation of CRC cells [79].

Small extracellular vesicles increase angiogenesis and vascular permeability in the pre-metastatic niche of colorectal cancer

Angiogenesis, the formation of new blood vessels from existing capillaries or post-capillary veins, is crucial for tumor growth and metastasis. Angiogenesis is vital not only for maintaining tumor growth, but also for initiating vascular development from tumor cells connecting to the existing circulatory system to enter the vascular system. Following vascular overgrowth, pro-

angiogenic factors, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), thrombospondin-1 (TSP-1), transforming growth factor (TGF), endothelial growth factor (EGF), and fibroblast growth factor (FGF), etc. are released to promote tumor growth and metastasis [80,81]. Furthermore, the increasing vascular permeability in the PMN of CRC serves as initial step in tumor development and subsequent metastasis. Certainly, sEVs play an important role in these steps (Table 3).

Nami et al. demonstrated that CRC-derived miR-92a-3p-containing sEVs induce partial EMT by downregulating Dickkopf-3 (an inhibitor of the Wnt pathway) and Claudin-11 (a cell tightly linked transmembrane protein) in HUVECs, thereby promoting angiogenesis [82]. Similarly, Zeng's et al. reported that CRC-secreted miR-25-3p can be delivered to vascular endothelial cells via sEVs, disrupting the integrity of the endothelial barrier and inducing angiogenesis, thereby promoting the liver and lung metastasis of CRC [83]. Additionally, Yin et al. found that CAFs-derived sEVs promote CRC cell growth and angiogenesis by upregulating microRNA-135b-5p via thioredoxin-interacting protein targeting thioredoxin-interacting protein (TXNIP) inhibition [84]. Similarly, the team of Hu found that miR-1229^{+}sEVs derived from CRC cells can promote angiogenesis by targeting HIPK2, thereby promoting the formation of pre-metastatic ecological sites and tumor progression [85]. Furthermore, Huang et al. reported that under hypoxic conditions, CRC cells promote endothelial cell angiogenesis through Wnt4-rich sEVs-mediated Wnt/β-catenin pathway transduction [86]. In a similar study, He et al. observed that miR-21-5p-containing sEVs secreted by CRC activate the β-linked protein signaling pathway by targeting Krev interaction trapped protein 1 (KRIT1), inducing angiogenesis and vascular permeability and consequently promoting tumor progression [87]. Moreover, Shang's team reported that CRC-secreted miR-183-5p-containing sEVs enhance angiogenesis in microvascular endothelial cells by targeting forkhead box O1 (FOXO1), thereby promoting CRC development [88]. Additionally, sEVs derived from lncRNA-APC1-silenced CRC cells promote angiogenesis by activating the MAPK pathway in endothelial cells [89]. Moreover, Chen et al. demonstrated that CRC-derived circTUBGCP4-containing sEVs promote tip cell formation and activate the Akt signaling pathway by inhibiting miR-146b-3p, causing vascular endothelial cell tilting, promoting angiogenesis and thereby affecting tumor metastasis [90]. Jiang's team showed that sEVs containing angiopoietin-like protein 1 (ANGPTL1) secreted by CRC attenuate CRC liver metastasis by inhibiting the JAK2-STAT3 signaling pathway, reprogramming Kupffer cells and reducing MMP9 expression to prevent vascular leakage in hepatic PMN [91].

These studies suggest the potential involvement of sEVs in angiogenesis and vascular permeability in promoting PMN formation and consequently tumor progression.

Small extracellular vesicles promote lymphangiogenesis and lymphatic network remodeling in the pre-metastatic niche

Similar to angiogenesis, lymphangiogenesis is the generation of new lymphatic vessels from preexisting lymphatic vessels or lymphatic endothelial progenitor cells [92]. Lymphangiogenesis and lymphatic network remodeling play an integral role in the PMN of tumors. Lymph node (LN) metastasis is a key prognostic indicator for disease staging, with the lymphatic system serving as an important route for metastatic spread in addition to hematogenous metastasis [93]. Related clinical studies indicate that tumor-derived VEGF-A and VEGF-D induce pro-metastatic lymphangiogenesis in regional LNs, thereby promoting the formation of lymphovascular niches in oral squamous cell carcinoma (OSCC) lymph nodes [94].

Lymphatic network remodeling has been demonstrated to affect tumor metastasis in the sentinel lymph node (SLN). Sun et al. found that CT26 cells secrete IRF-2-containing sEVs and induce macrophages to release VEGFC, thus promoting lymphatic endothelial cell proliferation and lymphatic networks formation in the SLN and further advancing SLN metastasis in CRC [95]. As an occluded conduit for the return of lymphatic fluid to the bloodstream, lymphatic vessels are key to the continued progression to CRC. Notably, the team of Zhang showed that miR-

Table 4. Other roles of sEvs in the pre-metastatic niche.

Characteristic	sEVs cargos	Tissues and/or cells	Mechanism and function	Refs
Lymphangiogenesis	IRF-2	CT26	Inducing macrophages to release VEGFC, thus promoting the proliferation of lymphatic endothelial cells and the formation of lymphatic network in SLN, and promoting SLN metastasis in colorectal cancer	95
Lymphangiogenesis	miR-302d-3p	Human Umbilical Cord Mesenchymal Stem Cells	Targeting FLT4 to inhibit lymphangiogenesis and macrophage infiltration to improve IBD	96
Organotropism	ITGα v β 5	HT29	Binds to Kupffer cells and mediates hepatophilic	29
Organotropism	ITGα 6 β 4′ ITGα 6 β 1	HT29	Binding of lung-resident fibroblasts and epithelial cells to control pulmonary eosinophilia	29
Organotropism	-	HT29 and Caco2	be associated with the SDF-1/CXCR4 axis	97
Organotropism	miR-135a-5p	CRC tissues	The hypoxic microenvironment in primary CRC lesions promotes the release of sEVs, which are phagocytosed by Kupffer cells into the liver′and miR-135a-5p^{+}sEVs initiate the large tumor suppressor kinase 2-yes-associated protein-matrix metalloproteinase 7 axis to promote the development of CRC liver metastases	98
Reprogramming	-	SW480;SW620	sEVs activate fibroblasts and invade the extracellular matrix, thereby advancing metabolic reprogramming	104
Reprogramming	HSPC111	HCT116′ HT29′SW480, SW620; CRC tissues	Reprogramming lipid metabolism in cancer-associated fibroblast CAF promotes pre-metastatic ecotone formation and liver metastasis in colorectal cancer	106
EMT	miR-128-3p	HCT116,SW480	miR-128-3p^{+}sEVs regulates EMT by directly suppressing its downstream target gene FOXO4 to activate TGF-β/SMAD and JAK/STAT3 signaling, and the properties of the miR-128-3p/FOXO4 axis were horizontally transferred via exosomal delivery.	113
EMT	circCOL1A2	HT29, HCT116, LOVO, SW480, and SW620	circCOL1A2^{+}sEVs mediated miR-665/LASP1 axis to affect the EMT and modulate CRC progression	114
EMT	PCAT1	HCT116,SW480	lncRNA PCAT1 Promotes Tumor Circulating Cell-Mediated Colorectal Cancer Liver Metastasis by Regulating the Activity of the miR-329-3p/Netrin-1-CD146 Complex	115
EMT	miR-335-5p	SW480,SW620	sEVs-encapsulated miR-335-5p promotes CRC cell invasion, metastasis, and EMT transition by directly targeting RASA1	116

302d-3p highly expressed in sEVs secreted by human umbilical cord mesenchymal stem cells (hucMSC) inhibits lymphangiogenesis and macrophage infiltration by targeting the Fms-related receptor tyrosine kinase 4 (FLT4) to improve inflammatory bowel disease (IBD) [96].

Small extracellular vesicles determine colorectal cancer organ metastasis

In the "seed and soil" theory, if tumor cells are considered the "seeds" and the PMN is the "soil", then sEVs can be equated are to fertilizers that facilitate the rooting and germination of seeds. This intricate and dynamic communication between the "seed" and the "soil" is known as organ orientation. Organ-oriented features have been speculated to be associated with the PMN because certain cancers tend to metastasize to specific organs with selective microenvironments [9]. Similarly, tumor-derived sEVs have been demonstrated to affect organotropy. For example, Hoshino et al. defined a specific integrin library expressed on tumor-derived sEVs. The authors found that sEVs expressing ITGαvβ5 specifically bind to Kupffer cells and mediate hepatophilia, whereas sEVs expressing ITGα6β4 and ITGα6β1 bind to lung-resident fibroblasts and epithelial cells and control pulmonophilia. Furthermore, sEVs in the blood tend to be captured by specific organs owing to the exosomal integrin pool, which in turn drives their binding to resident target cells [29]. These findings underscore the potential of circulating tumor-derived sEVs in predicting metastatic propensity and identifying the organ sites of future metastases. Additionally, Wang's group showed that activation of SDF1-mediated chemotaxis of stromal cells toward hepatic ecotopes is a potential mechanism of sEVs released from CRC cells [97]. It has been shown by Sun' team that the hypoxic microenvironment in primary CRC enhances the release of sEVs, selectively initiating favorable the formation of the PMN in the liver, but not in other organs [98]. Thus, sEVs will most likely begin to form PMN at those sites that allow them to anchor and fuse [99].

Small extracellular vesicles affect stromal cell activation and remodeling in the pre-metastatic niche

The survival of cancer cells at metastatic sites is highly dependent on the stromal microenvironment, which is composed mainly of fibroblasts, endothelial cells, and ECM in the PMN [100]. Many studies have demonstrated that metabolic reprogramming, matrix reprogramming and epigenetic reprogramming are associated with the PMN [101,102].

Fibroblasts not only produce inflammatory factors and growth factors, but also express fibronectin (FN) and matrix metalloproteinases (MMP) [103]. CAFs, major cellular components of the tumor microenvironment, are a heterogeneous population of activated fibroblasts with different functions. Alin Rai et al. analyzed the role of primary and metastatic CRC tumor-derived sEVs in generating phenotypically and functionally distinct subpopulations of CAF that promote tumor progression. Moreover, primary tumor-secreted sEVs-activated fibroblasts were highly proliferative and pro-angiogenic. However, fibroblasts activated by sEVs secreted by metastatic tumors showed a striking ability to invade through the ECM by upregulating pro-invasive regulators of membrane protrusion (PDLIM1, MYO1B) and matrix-remodeling proteins (MMP11, EMMPRIN, ADAM10) advancing metabolic reprogramming and further promoting CRC metastasis [104]. Similarly, based on protein mass spectrometry analysis, Alin Rai's team also proposed that sEVs upregulate fibroblast proteins associated with focal adhesion (ITGA2/A6/AV, ITGB1/B4/B5, EGFR, CRK), actin cytoskeleton regulators (RAC1, ARF1, ARPC3, CYFIP1, NCKAP1, ICAM1, ERM complex), and signaling pathways important in the aggressive remodeling of the ECM(MAPK, Rap1, RAC1, Ras), illustrating the relevance of fibroblasts in the process of ECM remodeling [105].

HSPC111 is a major upregulated gene in hepatic stellate cells (HSC) incubated with CRC cell-derived sEVs. Recently, it was found by Zhang's group that CRC cell-derived sEVs with high HSPC111 expression, promote the PMN

formation and CRC liver metastasis by reprogramming lipid metabolism in CAFs. Mechanistically, sEVs HSPC111 convert fibroblasts into CAFs and phosphorylate ATP-citrate lyase (ACLY) to increase acetyl coenzyme levels in CAFs in the PMN of the liver. Moreover, increased CXCL5 secretion via the CXCL5-cxcr2 axis was demonstrated to promote EMT and metastasis of CRC cells [106].

Recently, Kylie G Nairon et al. constructed models to simulate the PMN (biologically manufactured collagen and hyaluronic acid hydrogel models), using CRC cell lines. They found that tumor-secreted correlates can drive collagen remodeling through pericyte and fibroblast activation. This research has given new ideas to the mechanisms related to tumor and the PMN [107]. Of course, the role played by sEVs in the PMN has been explored more deeplyTable 4.

Involvement of small extracellular vesicles in the epithelial-to-mesenchymal transition in pre-metastatic niche of colorectal cancer

A critical link between the pre-metastatic niche maturation and the onset of tumor metastasis, ECM remodeling, molecular constituents such as IL-1b [108] and regulatory immune cells such as MDSCs [109], may induce the EMT, confer stemness to tumor cells, and promote tumor cell invasiveness. EMT is considered to be a prerequisite for initial tumor cell motility and acquisition of invasiveness, leading to metastasis and recurrence in many cancer types [110]. During EMT, epithelial tumor cells undergo significant morphological and phenotypic changes, including loss of tight junctions, cell polarity, and cytoskeletal reorganization, to transform into an aggressive phenotype (mesenchymal cells) that promotes cancer motility, metastasis, and progression [111,112].

Bai et al. demonstrated that sEVs containing miR-128-3p secreted by CRC inhibits its downstream target gene FOXO4, which, in turn, activates the TGF-β/SMAD and JAK/STAT3 signaling pathways to regulate EMT. This pro-EMT property of miR-128-3p can be transferred to neighboring CRC cells via sEVs delivery to further influence EMT-related CRC progression [113]. Miao et al. investigated the role of circular RNAs (circRNAs) in CRC, revealing that sEVs derived from CRC highly expressed circCOL1A2 and regulated the miR-665/LASP1 signaling axis affecting the EMT, which further affects the progression of CRC [114]. Fang's group found that PCAT1, a IncRNA derived from CRC sEVs, regulates the activity of the Netrin-1-CD146 complex in CTCs and promotes the EMT and liver metastasis in CRC [115]. Similarly, Sun et al. showed that miR-335-5p^{+}sEVs derived from metastatic CRC cell line SW620 promoted CRC cell invasion and metastasis by targeting RASA1 to promote EMT [116].

However, the roles that sEVs play in the PMN remain to be further explored (Table 4).

Related applications of small extracellular vesicles in the pre-metastatic niche

Owing to the specificity of the lipid bilayer membrane structure, sEVs tend to maintain the stability of their loaded cargos. Moreover, the rich variety of sEVs, coupled with their tumor specificity, makes sEVs uniquely advantageous as biomarkers of the PMN formation. Notably, sEVs can serve cas noninvasive biopsy specimens for cancer detection and prognosis in clinical settings.

Liquid biopsy, a minimally invasive method for early detection, analyses CTCs, circulating tumor cells, free nucleic acids and tumor-derived EVs from blood, urine, cerebrospinal fluid, pleural fluid and ascites to analyze the disease and guide clinical diagnosis and treatment [117]. Notably, the first cancer diagnostic product using sEVs was launched in the US on January 21, 2016 [118]. Since then, there has been an increase in studies on sEVs. For instance, state-of-the-art biosensors in liquid biopsies detect sEVs of cancer origin through highly specific target selection, antigen sensing, and signal transduction techniques [119]. As sEVs are rich in VEGF-A, signalin-3A, and TGF-β in glioma (GBM), HIF1-αin nasopharyngeal carcinoma, and MT1 MMP in fibrosarcoma and melanoma [120], these molecules are promising targets for liquid biopsies, as well as important markers in disease progression. In CRC, Hu's team detected that a high expression of CAF-sEVs miR-92a-3p in serum samples

associated with metastasis and chemoresistance [121]. Therefore, Rahul Bhome et al. report that CAF-sEVs microRNAs are considered as a promising potential biomarker based on their characteristics to regulate tumor cell proliferation and drug resistance [122]. Circulating endothelial cells (CEC) are rarely observed in healthy individuals but can often be detected in patients with cancer. Their use in treatment response monitoring is a promising clinical tool [123]. In CRC patients, CEC quantification improves the identification of early predictors for the efficacy of bevacizumab in combination with FOLFOX (FOL-folic acid (folinic acid), 5-fluorouracil (5-FU), OX-oxaliplatin (Eloxatin)/OXXEL (oxaliplatin plus Xeloda) [124].

As a delivery system, sEVs can deliver proteins, miRNAs or short interfering RNAs that specifically regulate target genes involved in tumor progression to improve cancer therapy [125]. At the same time, sEVs can be loaded with drugs and transported to the desired target, thus becoming a new therapeutic tool. For example, Abak et al. demonstrated the efficacy of adriamycin and paclitaxel loaded into sEVs in reducing tumor progression in CRC and other tumor types [126]. It has been shown by Senthilkumar Kalimuthu et al. that synthetic exosome mimics loaded with paclitaxel to inhibit breast tumor growth, with therapeutic notes in both in vitro and in vivo experiments [127].

Discussion, conclusion, and prospects

Based on the hypothesis of Cao et al. [9], the PMN can be considered as an ordered time sequence of pathological events. In the priming phase, the primary tumor begins to proliferate uncontrollably, inducing hypoxia and inflammation occurs. Moreover, during this process, various molecular components are produced, such as EVs, that induce the mobilization of bone marrow-derived dendritic cell (BMDCs) and regulatory/suppressor immune cells to future metastatic organs and initiate the reprogramming of the host stromal environment in distant organs. In the licensing phase, immune cells are constantly mobilized and recruited to secondary sites, owing to stimulation by various molecules. The induction of matrix remodeling and activation of integrins and chemokines influence these secondary, minor sites to support the formation of the PMN, which includes EMT development. In the Initiation phase, the colonization of CTCs into the ecotone is promoted through angiogenesis. In the progression phase, an increasing number of tumor cells continue to leave the primary site and colonize the mature PMN of the metastatic organ.

From the literature, the salient characteristics of the cPMN, ranging from inflammatory responses to organotropisms, were found to be not mutually exclusive or sequentially progressive. These events are integrated and act synergistically, forming a tacit microenvironment that promotes tumor development and metastasis. The establishment of the PMN is essential for tumor metastasis and elucidating its role in a more in-depth manner holds potential in controlling tumor progression. However, sEVs play a unique role in regulating the PMN and subsequent progression of CRC. Notably, owing to their biological properties, sEVs can be used in the targeted delivery of oncology drugs or can be modified as biomarkers, vaccines, and drug carriers. However, the isolation and extraction of sEVs require further study to improve its specificity and sensitivity. Moreover, the PMN in CRC-metastatic deserves further exploration as there remain many unanswered questions. For example: do all types of CRCs undergo metastasize? Is an inflammatory or hypoxic CRCs undergo required for metastasis to occur? Is there a causal relationship between the tumor microenvironment of primary CRC and the PMN formation in the initiation of metastasis? What is the specific role of EVs in this? What we can say with certainty is that the mechanistic role of sEVs in CRC metastasis remains to be studied more.

Therefore, understanding the intricate role of sEvs in CRC metastasis opens new avenues for diagnosis, treatment and prognosis.

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