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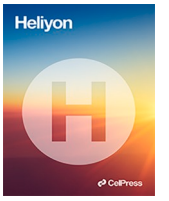

Review article

Exosomes promote pre-metastatic niche formation in colorectal cancer

Guifei Si [a], Xuemei Chen [a], Yuquan Li [a], Xuemin Yuan [b,*]

[a] School of Clinical Medicine, Weifang Medical University, Weifang, Shandong, 261000, China
[b] Department of Gastroenterology, Linyi People's Hospital, Linyi, Shandong, 276000, China

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ABSTRACT

It is well known that colorectal cancer (CRC) has a high morbidity rate, a poor prognosis when metastasized, and a greatly shortened 5-year survival rate. Therefore, understanding the mechanism of tumor metastasis is still important. Based on the "seed and soil" theory, the concept of " premetastatic niche (PMN)" was introduced by Kaplan et al. The complex interaction between primary tumors and the metastatic organ provides a beneficial microenvironment for tumor cells to colonize at a distance. With further exploration of the PMN, exosomes have gradually attracted interest from researchers. Exosomes are extracellular vesicles secreted from cells that include various biological information and are involved in communication between cells. As a key molecule in the PMN, exosomes are closely related to tumor metastasis. In this article, we obtained information by conducting a comprehensive search across academic databases including PubMed and Web of Science using relevant keywords. Only recent, peer-reviewed articles published in the English language were considered for inclusion. This study aims to explore in depth how exosomes promote the formation of pre-metastatic microenvironment (PMN) in colorectal cancer and its related mechanisms.

1. Introduction

Colorectal cancer is one of the most common malignancies in the world. In recent years, in the United States, colorectal cancer mortality and incidence rates have dropped, while in China, the mortality and incidence rates have dramatically increased. Overall, colorectal cancer remains the second leading cause of cancer death in the world [1]. The liver is the most frequently site of metastasis for colorectal cancer [2]. Tumor metastasis is the main cause of poor prognosis and death. The 5-year survival rate for patients with early-stage CRC can be as high as 90%; however, when distant metastasis occurs, the 5-year survival rate decreases to 11%–15% [3]. The mainstay of treatment for patients with colorectal liver metastases is resection and chemotherapy. Unfortunately, only 10–20% of colorectal liver metastases cases are eligible for resection when diagnosed [4]. Despite progress and optimization of chemotherapy regimens, colorectal liver metastases patients that receive fluorouracil and platinum-based chemotherapy, will eventually develop side effects, resistance and toxicity [5]. Therefore, for colorectal liver metastases, it is extremely urgent to develop more effective targeted therapies. Understanding the molecular mechanisms involved in the process of colorectal liver metastases development may achieve this objective.

Tumor metastasis is summarized into two phases. The first phase refers to the immigration of tumor cells from the original tumor to

* Corresponding author.
E-mail addresses: sgf2498@163.com (G. Si), 295501487@qq.com (X. Chen), 3177567840@qq.com (Y. Li), wdxuemin0707@126.com (X. Yuan).

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the target organ, which is also known as physical metastasis; the second phase refers to the ability of cancer cells to colonize and metastasize within the target organ [6]. Paget et al. was the first to suggest the "seed and soil" theory in the last century, comparing tumor cells dispersed early to "seeds" and planting organs as fertile "soil" suitable for the growth and reproduction of "seeds" [7]. Based on this concept, Kaplan et al. introduced the idea of the "premetastatic niche (PMN)" [8]. The complex interaction between primary tumor cells and secondary organs creates a microenvironment conducive to distant colonization of tumor cells [9], providing new advances in the study of tumor metastasis. The interaction of various cellular components or cytokines, such as extracellular matrix (ECM), exosomes, tumor-derived secreted factors (TDSFs), and bone marrow-derived cells (BMDCs), is strongly associated to the formation of PMNs [10,11].

The mechanisms for how PMN formation occur prior to the arrival of tumor cells are unidentified. It appears that tumor-associated exosomes are good mediators of this remote regulation [12,13]. In 1981, EG Trams discovered extracellular vesicles in sheep reticulocytes [14]. In 1987, Johnstone officially named this type of vesicle as an exosome [15]. The morphology of exosomes is cup-shaped or disk-shaped with a density of 1.13–1.19 g/ml and a diameter of approximately 50–100 nm [16]. Hsp70, Tsg101, β1-integrin, Aip1, Cd63, and Cd81 are typical biomarkers for exosomes [17]. Exosomes are isolated from urine, plasma and serum [18–21]. Almost all cells produce exosomes, but different types and sources of cells produce different types and amounts of exosomes [22]. Cancer cells produce more exosomes than normal cells [23,24]. Exosomes were originally thought of as a cellular "garbage dumpster"(removing unwanted material from cells). However, as research progressed, they have been shown to be important mediators of cell-to-cell communication [25–30].

Pioneering studies have shown that platelet-derived exosomes induce metastasis and angiogenesis in breast and lung cancers [31, 32]. Nevertheless, these studies did not evaluate the role of exosomes in PMN formation. Since then, Peinado et al. proposed that exosomes may be involved in the formation of PMN [33]. Jung and Kaplan et al. demonstrated that exosomes are pivotal companions for soluble factors' initiating pre-metastatic niche [8,34]. As research continues, accumulating studies have demonstrated that tumor cell-derived exosomes can be delivered to distant metastatic organs prior to the arrival of tumor cells. Upon reaching distant metastatic organs, they promote angiogenesis, enhance vascular permeability through intracellular substances, induce inflammatory cells, and recruit myeloid-derived suppressor cells [27,30,35,36]. This process creates a beneficial PMN that facilitates the growth of disseminated cancer cells [37]. According to recent studies, tumor-derived exosomes are an essential component of the liver microenvironment. They contribute to the formation of hepatic PMN, which promotes liver-specific metastases [35,38]. According to current research, exosomes mediated pathways of hepatic PMN formation include promoting the formation of an inflammatory and immunosuppressive microenvironment, inducing vascular and lymphatic remodeling, mediating organotropism and reprogramming [10, 35]. In addition, tumor-derived exosomes can be considered as latent biomarkers and may provide a novel approach for the development of therapeutics for liver metastatic cancer [27,39,40]. Although exosomes have been widely studied, their role in hepatic PMN formation has not yet become systematic. This remains an area that needs to be further researched.

In this review, we summarize the effect of exosomes in the formation of the micro-environment before hepatic transfer of CRC. In particular, we focused on how exosomes play a role in intercellular communication and the regulation of the tumor microenvironment, thereby deepening our understanding of the tumor metastasis process. By revealing these key processes, this study is not only expected to provide new perspectives for the early diagnosis and treatment of colorectal cancer, but may also reveal new biomarkers and therapeutic targets, which have important implications for the development of anti-cancer strategies.

2. Methods

In conducting the literature review for this study, we adopted an exhaustive search strategy to ensure comprehensiveness and relevance. We mainly used two databases, PubMed and Web of Science, for literature search. In order to accurately locate the relevant literature, we selected keywords including 'exosomes',' colorectal cancer 'and' pre-metastatic microenvironment 'for search. In addition, we set certain screening criteria, such as including only research papers published within the last five years and giving preference to peer-reviewed journal articles. Through this search strategy, we ensure the timeliness and scientific content of the review and provide a solid literature support foundation for our research.

This study followed strict criteria in selecting the literature for inclusion. First, we considered only those papers that made significant contributions to colorectal cancer and exosome research, particularly those that focused on the role of exosomes in the tumor microenvironment. Second, the included studies must have been published within the last five years and have been peer reviewed. In addition, we pay special attention to studies that demonstrate a high degree of rigor in their experimental design and data analysis. Through this process, we ensure the quality and relevance of the included research, providing a solid foundation for our research.

In the studies covered in this review, we examined a variety of different types of research models in detail. These models include cell line experiments conducted in vitro, such as studies using human colorectal cancer cell lines, as well as animal models used in vivo, particularly mouse models targeting tumor growth and metastasis. We also considered studies that used in vitro culture techniques, such as 3D cell culture and organ-on-a-chip technology, to better simulate the tumor microenvironment. By combining these different research models, we were able to fully understand the role of exosomes in colorectal cancer and how these findings might translate into clinical applications.

3. Epithelial-mesenchymal transition (EMT)

Before we can delve into the effect of epithelial-mesenchymal transition (EMT) on the formation of the colorectal cancer pre-metastatic microenvironment (PMN), we first need to understand the fundamental role of EMT in tumor metastasis. EMT is the process

of the transformation of tumor cells from primitive phenotype to mesenchymal cell phenotype, which plays a key role in the initial migration stage of tumors [41]. EMT is distinguished by decreased expression of E-cadherin and loss of cellular connectivity; during EMT, cytoskeletal rearrangement and N-cadherin expression are upregulated, and tumor cell invasion ability is enhanced (Fig. 1) [42–44,].In liver metastasis of colorectal cancer, the occurrence of EMT is closely related to the regulation of exosome secretion [45]. Therefore, this chapter will explore in detail the role of EMT in tumor cell metastasis and PMN formation, as well as how exosomes regulate this process, thereby deepening our understanding of the mechanisms of colorectal cancer metastasis.

Studies have shown that EMT occurs during colorectal cancer liver metastasis [6]. A recent study has demonstrated that exosome ADAM17 is overexpressed in the serum of metastatic colorectal cancer and that it enhances the expression of vimentin, N-cadherin, and Snail but increases the cleavage of E-cadherin, thereby promoting the occurrence of EMT in CRC and effectively enhancing the liver metastasis ability of CRC [46]. Translocation of exosomes produced by cancer-associated fibroblasts (CAFs) to CRC cells upregulated miR-92a-3p expression in CRC cells. Increased expression of miR-92a-3p contributed to EMT, metastasis, cell stemness and 5-FU/L-OHP resistance in CRC by directly inhibiting MOAP1 and FBXW7, thereby activating the Wnt/β-protein route and suppressing mitochondrial apoptosis [47]. A previous study has found that exosomal lncRNA PCAT1 expression is significantly increased in CRC tissues. PCAT1 causes overexpression of Netrin-1-CD146 by downregulating miR-329-3p, which promotes the formation of EMT, thereby enhancing CRC cell invasion and liver metastasis [48]. RASA1 has been transfected into SW480 cells and verified by protein imprinting and real-time PCR detection, demonstrating increased E-cadherin, decreased vimentin, and decreased migration and invasion ability. Overexpression of exosomal miRNA-335-5p in SW620 cells promotes metastasis and invasion of CRC cells by targeting RASA1 to enhance EMT [49]. A previous study has shown that CRC cells overexpress exosomal miR-128-3p, which induces the activation of the JAK/STAT3 and TGF-β/SMAD signaling pathways as well as suppressed FOXO4 expression in CRC cells, contributing to the development of EMT [50]. In SW620 and HCT8 cells overexpressing lncRNA RPPH1, E-cadherin expression is reduced, while N-cadherin and vimentin expression are raised; however, knockout of lncRNA RPPH1 results in opposite effects, suggesting lncRNA RPPH1 overexpression induces EMT. In addition, lncRNA RPPH1 binds to TUBB3 and activates the Snail pathway to achieve the abovementioned effects [51]. However, it remains unclear how TUBB3 activates the Snail pathway and participates in EMT formation, thereby requiring further study. Recent research has identified that the interactions between exosomes and macrophages are involved in the EMT process. Exosomal miR-106b-5p secreted by EMT tumor cells promotes macrophage polarization to the M2 type by downregulating PDCD4. M2 macrophages promote EMT in colorectal cancer cells through positive feedback, thereby further promoting liver metastasis of colorectal cancer [52]. In addition, exosomal miR-130b-3p, miR-425-5p and miR-25-3p can be transferred to macrophages, which regulates PTEN by triggering the PI3K/Akt signaling route, thereby inducing M2 polarization and strengthening EMT [53]. These observations emphasize a significant impact of exosomes on EMT development. Understanding the mechanisms of exosomes mediated EMT in a hepatic PMN is crucial.

4. Exosomes promote the development of the microenvironment before liver metastasis of colorectal cancer

Before exploring how exosomes promote the development of the premetastatic microenvironment in colorectal cancer, we need to clarify the role of exosomes in the tumor microenvironment. As an important medium of intercellular communication, exosomes play a key role in regulating the interaction between tumor cells and the surrounding microenvironment. This chapter will focus on how exosomes promote liver metastasis in colorectal cancer by carrying bioactive molecules such as miRNAs and proteins that promote the

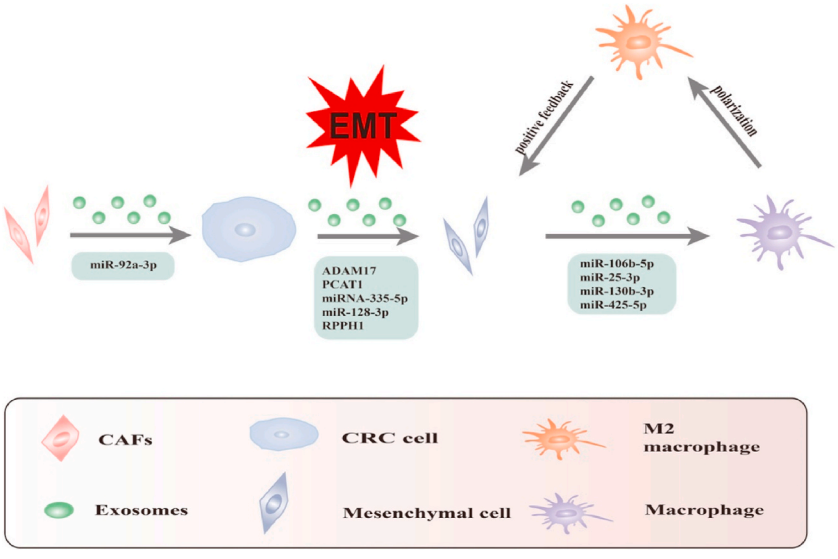

Fig. 1. Schematic of the role of exosomes in EMT formation. Exosomes affect EMT formation and enhance tumor aggressiveness. EMT, epithelial-mesenchymal transition; CRC, colorectal cancer; CAFs, cancer-associated fibroblasts.

development of a pre-metastatic microenvironment. By gaining a deeper understanding of these mechanisms, we are able to better uncover potential therapeutic targets for colorectal cancer metastasis.

4.1. Immunosuppression

The immune system is intimately involved in the development and migration of cancers. Classical monocytes facilitate cancer development and migration; however, NK cells, $CD8^+$ T cells, and "patrol" monocytes produce an antitumor immune response to prevent tumor metastasis [54,55]. To evade immune monitoring, tumor cells promote the polarization of normal immune cells to the protumor state and recruit suppressor immune cells, including myeloid-derived suppressor cells (MDSCs), tumor-associated neutrophils (TANs), tumor-associated macrophages (TAMs), and Tregs, to reach the metastatic site and form an immunosuppressive microenvironment to prepare for tumor transfer (Table 1) [56]. Exosomes have a strong relationship with these cells. MDSCs are mainly made up of immature myeloid cells (IMCs) with immunosuppressive functions [57]. Differentiation of hematopoietic stem cells and progenitor cells into MDSCs to facilitate the formation of an immunosuppressive microenvironment prior to tumor metastasis [58]. MDSCs mediate hepatic immunosuppression and promote the formation of PMNs with TNFR-2 support [59]. Exosomes secreted by tumor cells induce the expansion, recruitment, and immunosuppression of MDSCs in metastatic organs [60]. Chalmin F et al. found that the surface of exosomes released by CRC in mice expresses Hsp72, allowing production of IL-6 through an autocrine mechanism that relies on the TLR2-MyD88 pathway to trigger Stat3 phosphorylation in MDSCs, thereby promoting immunosuppression of MDSCs but not amplifying MDSCs. In parallel, Hsp72 was identified in exosomes secreted by human cancer cells. Hsp72 activates Stst3 in human MDSCs via Hsp72/tlr2 dependence and exerts its immunosuppressive function [61]. In summary, Hsp72 is shown on the surface of both mouse and human tumor-derived exosomes, which promotes MDSC immunosuppression and further inhibits tumor

Table 1
The role of exosomes in PMN formation in colorectal cancer.

Primary cancer	Phenotype	Contents in exosomes	Specific mechanism	References
CRC	Immunosuppression	Hsp72	TDEs from mouse cell lines activate Stat3 in MDSCs in a TLR2/MyD88-dependent manner through autocrine production of IL-6; TDEs from human tumor cell lines activate human MDSCs in an Hsp72/TLR2-dependent manner	[61]
		miR-934	Inducing M2 polarization of macrophages via downregulation of PTEN expression and activation of the PI3K/AKT signaling pathway	[62]
		miR-1246	Inducing macrophage polarization to M2; upregulating IL-10, TGF-β, and MMPs; recruiting Tregs	[63]
		circ PACRGL	Differentiation of N1 to N2 neutrophils via the miR-142-3p/miR-506-3p-TGF-β1 axis	[64]
		KCNQ1OT1, miR-17-5p, circEIF3K	Upregulating PD-L1 and inhibiting T cell proliferation	[65–67]
		miR-203a-3p	Downregulation of PTEN expression and activation of the PI3K/AKT signaling pathway induce M2 polarization, subsequently, tumor metastasis is promoted by the CXCL12/CXCR4/NF-κB axis	[68]
	Inflammation	miR-21	Inducing an inflammatory premetastatic niche through the miR-21–TLR7–IL-6 axis	[69]
		ITGBL1	Fibroblasts are activated by the EVs-ITGBL1-CAFs-TNFAIP3-NF-κB signaling axis and secrete inflammatory mediators	[70]
		miR-135a-5p	Phagocytosis by Kupffer cells, triggering the LATS2-YAP-MMP7 axis and secretion of inflammatory mediators	[71]
		miR-181a-5p	Targeting SOCS3 and activating the IL6/STAT3 signaling pathway induces HSC activation and promotes CCL20 secretion; the CCL20/CCR6/ERK1/2/Elk-1/miR-181a-5p positive feedback pathway was used to promote the formation of PMN for colorectal cancer liver metastasis.	[72]
	Angiogenesis	miR-25-3p	Upregulating EC expression of VEGFR2 and downregulating the level of occludin, ZO-1, and Claudin5 by silencing KLF2/KLF4	[73]
		ANGPTL1	Regulating the secretion pattern of Kupffer cells by inhibiting the JAK2-STAT3 signaling pathway and decreasing MMP9 expression to prevent vascular leakiness	[74]
	Lymphangiogenesis	IRF-2	Upregulating VEGF-C to promote the formation of a lymphatic network in SLN	[75]
	Organotropism	ITG$\alpha_v\beta_5$, $\alpha_v\beta_6$, $\alpha_6\beta_4$, $\alpha_6\beta_1$	ITG $\alpha_v\beta_5$ and $\alpha_v\beta_6$ are associated with liver metastasis, while integrins $\alpha_6\beta_4$ and $\alpha_6\beta_1$ are related to lung metastasis	[76]
	Reprogramming	HSPC111	Upregulating acetyl-CoA, promoting CXCL5 expression and secretion, and reprogramming lipid metabolism in CAFs	[77]
		No specific	Enhancing CRC aggressiveness and metastatic capacity by reprogramming CAF amino acid metabolism	[78]
		101-3p	Targeting HIPK3, reducing ROS levels, and reprogramming colorectal cancer metabolism	[79]

Abbreviations: CRC, colorectal cancer; TDEs, tumor-derived exosomes; MDSCs, myeloid-derived suppressor cells; TLR2, toll-like receptor 2; TLR7, toll-like receptor 7; IL-6, interleukin-6; IL-10, interleukin-10; MMPs, matrix metalloproteinases; TGF-β, transforming growth factor β; PD-L1, programmed death-ligand 1; CAFs, cancer-associated fibroblasts; ITGBL1, integrin beta-like 1; EVs, extracellular vesicles; ANGPTL1, angiopoietin-like protein 1; MMP7, matrix metalloproteinase 7; MMP9, matrix metalloproteinase 9; VEGFR2, vascular endothelial growth factor receptor 2; VEGF-C, vascular endothelial growth factor C; SLN, sentinel lymph node; ITG, integrin; ROS, reactive oxygen species.

immune surveillance.

Macrophages have two phenotypes, namely, M1 and M2, of which M1 (proinflammatory) inhibits tumors and M2 (anti-inflammatory) promotes tumors. TAMs are mainly M2 macrophages [80]. In CRCs, hnRNPA2B1 binds to the GGAG sequence, mediating the transfer of exosomal miR-934 secreted by CRCs to macrophages. Subsequently, exosomal miR-934 evoked macrophage polarization to the M2 phenotype by down-regulation PTEN expression and activating the PI3K/AKT signaling pathway. Polarized M2 macrophages secrete a variety of cytokines and chemokines to induce the development of an immunosuppressive microenvironment. The transcription of miR-934 in CRC cells is promoted through the CXCL13/CXCR5/NFκB/p65/miR-934 positive feedback pathway, further maintaining M2 polarization, thereby inducing the establishment of an immunosuppressive hepatic microenvironment and contributes to the hepatic metastasis of CRC. Furthermore, the expression level of plasma exosome miR-934 is positively linked to hepatic metastasis and prognosis of CRC. Therefore, miR934 is potentially a biomarker for forecasting CRC migration and prognosis in the future, and it may also be considered as a targeted therapy [62]. In addition, Pei et al. also demonstrated in a cell experiment that the exosomal miR-203a-3p is also associated with macrophage polarization. It could induce M2 polarization through downregulation of PTEN expression and activation of the PI3K/AKT signaling pathway. Polarized M2 macrophages secrete CXCL12, which promotes tumor metastasis through the CXCL12/CXCR4/NF-κB axis and mediates the formation of PMN for colorectal cancer liver metastasis [68]. Cooks et al. found that CRC cells containing the TP53 mutant (mutp53) secrete exosomal miR-1246, which is phagocytosed by macrophages, inducing macrophage reprogramming and polarization into M2 macrophages. It produces anti-inflammatory factors and tumor-supporting factors (IL-10, TGF-β, and MMPs), which induce the production of an inflammatory microenvironment, recruit Tregs cells to produce immunosuppression, and promote the progression of CRC [63].

Neutrophils are similar to macrophages and have N1 and N2 types. Of which, N1 has antitumor activity, and N2 has tumorigenicity. TANs are mainly N2 [81,82]. Neutrophils polarize to N2 under the action of exosomes, inducing immune escape and promoting tumor progression. Recent research has reported that the exosomal circPACRGL secreted by CRC acts as a sponge for miR-142-3p and miR-506-3p, which share a common destination, namely, TGF-β1. The high expression of TGF-β1 promotes the conversion of N1 to N2. Thus, circPACRGL induces neutrophil polarization to TANs and facilitates proliferation, immigration and invasion of CRCs by regulating the miR-142-3p/miR-506-3p-TGF-β1 axes [64].

Recently, programmed death ligand 1 (PD-L1)-induced immune escape in tumor cells has attracted widespread attention. PD-L1 on the surface of cancer cells combines with PD-1 on the surface of T cells to inhibit T cell proliferation, causing T cell inactivation, and hindering T cells from recognizing and attacking tumor cells [83]. PD-L1 also exists in tumor-secreted exosomes, which have the same structure and function as PD-L1 on the surface of cancer cells, and it is also combined with PD-1 on the surface of T cells induces apoptosis of T cells, produce immunosuppression, and induce Immunology evasion of cancer cells [84,85]. In CRC, tumor-derived exosomes highly express lncRNA KCNQ1OT1 through autocrine action. LncRNA KCNQ1OT1 regulates PD-L1 ubiquitination, suppresses the $CD8^+$ T cell immune function, induces colorectal cancer immune escape, and promotes CRC metastasis by mediating the miR-30a-5p/USP22 route [65]. In a mouse model, it has been shown that colorectal cancer stem cell exosomal miR-17-5p targets SPOP, upregulates PD-L1, inhibits the antitumor immune response, and promotes CRC metastasis [66]. Hypoxia stimulates CAF secretion of exosomal circEIF3K, which upregulates PD-L1 by targeting miR-24 and promotes CRC transfer [67]. When exosomes carry PD-L1 to the PMN, the immune system is suppressed, forming an immunosuppressive microenvironment and promoting cancer colonization and transfer [86].

4.2. Inflammation

The inflammatory microenvironment is an instrumental factor in establishing PMN (Table 1). Chronic inflammation enhances to tumor evolution and development by inducing epigenetic changes, genetic mutations, and physiological instability [87]. The native inflammatory microenvironment triggers cancer cells to secrete tumor-derived secreted factors (TDSFs), for example interleukin (IL), tumor necrosis factor alpha (TNF-α), vascular endothelial growth factor (VEGF), and transforming growth factor-β (TGF-β), participating in the formation of PMNs [86]. Exosomes participate in the upregulation of inflammation-activating factors and pro-inflammatory cytokines during the setting up of an inflammatory environment in organs to which cancer will metastasize [88]. It has been shown that exosomal miR-21 secreted by CRC cells is taken up by liver macrophages. The ingestion of miR-21 promotes the polarization of Kupffer cells to the proinflammatory phenotype by activating the TLR7 pathway, further enhancing the expression of Csf3, S100A8, and IL-6, which promotes the development of a hepatic inflammatory microenvironment under the action of the miR-21-TLR7-IL-6 axis, ultimately providing beneficial circumstances for the metastasis of CRC to the liver [69]. Thus, miR-21 levels are used as a biological marker to predict poor prognosis and recurrence in patients with CRC liver metastases in different stages [89]. In addition, studies have demonstrated that exosomal ITGBL1 is strongly expressed in advanced CRC and is closely related to CRC transfer. ITGBL1 secreted by CRC cells binds to TNFAIP3 and activates the NF-κB signaling route to convert liver fibroblasts into cancer-associated fibroblasts (CAFs). CAFs secrete proinflammatory factors, such as IL-8 and IL-6, to enhance CRC cell aggressiveness and contribute to the development of the microenvironment pre-liver migration in CRC [70]. The hypoxic microenvironment induces exosomal miR-135a-5p release from CRC cells. miR-135a-5p selectively reaches the liver through blood circulation and is absorbed by Kupffer cells. Subsequently, miR-135a-5p activates the LATS2-YAP-MMP7 axis to release inflammatory mediators, forming an inflammatory microenvironment and promoting liver metastasis of CRC. In addition, CD30-TRAF2-p65 mediates immunosuppressive signals to promote the formation of the above processes [71]. According to Zhao et al., miR-181a-5p was found to be abundant in exosomes of highly metastatic CRC cells. By targeting SOCS3 and activating the IL6/STAT3 signaling pathway, miR-181a-5p can induce the activation of hepatic stellate cells (HSCs). HSCs could secrete the CCL20. CCL20 can promote the formation of PMN in colorectal cancer liver metastases through the CCL20/CCR6/ERK1/2/Elk-1/miR-181a-5p positive feedback pathway [72]. These

studies indicate that exosomes, as tumor secretory factors, play a key role in the release of pro-inflammatory factors that promote the establishment of PMN in the liver.

4.3. Vascular permeability/angiogenesis

Angiogenesis and enhanced vascular permeability are important features of PMN formation, which promote the arrival of circulating tumor cells at the location of transfer, providing essential nutrients and oxygen for tumor growth [90]. Exosomes have an essential effect in enhancing vascular permeability and promoting angiogenesis (Table 1) [73]. Vascular endothelial cadherin (VE-Cad) and p120-catenin (p120) are important factors in maintaining vascular integrity [44]. In addition, E-cadherin is expressed on the surface of exosomes and induces cancer angiogenesis [91]. Neovascularization transports TDSF, exosomes, and circulating tumor cells to specific sites of metastasis, subsequently promoting enhanced vascular osmosis under the action of exosomes [86]. It is well-established that vascular endothelial cells (ECs) play a critical role in vascular remodeling [88]. Compared to nonmetastatic CRC patients, the expression of exosomal miR-25-3p in patients with metastases is clearly upregulated and positively related to the level of paracancerous endothelial cells, and the level of serum exosomal miR-25-3p is relevant to CRC progression and prognosis. In a murine model, exosomal miR-25-3p has been demonstrated to be transferred to vascular endothelial cells. By aiming KLF2 and KLF4, exosomal miR-25-3p reduces the expression of downstream targets, including occludin, ZO-1, and claudin-5, and enhances the expression of VEGFR2, thereby destroying the vascular endothelial barrier, inducing neoangiogenesis, and enhancing the hepatic metastasis and pulmonary metastasis of CRC in mice [73]. However, recent research has indicated that certain exosomes can inhibit the angiogenesis of PMN and hinder tumor metastasis. Angiopoietin-like protein 1 (ANGPTL1) is poorly expressed in CRCs compared to normal colorectal tissue. Exosomal ANGPTL1 secreted by CRC is transferred to Kupffer cells by regulating Kupffer cell secretion patterns, which inhibits the JAK2-STAT3 signaling pathway, further reducing the expression of MMP9, reducing hepatic vascular permeability, and inhibiting liver metastasis of CRC [74]. In summary, the role of exosomes secreted by CRC cells in vascular remodeling in PMN is still enormous controversial. In the future, this will continue to be a direction worth exploring.

4.4. Lymphangiogenesis

In most tumors, lymph node metastasis is considered as an independent prognostic factor [88]. Lymphatic vessels may be the initial process of tumor lymphatic migration, and lymphangiogenesis in the premetastatic microenvironment promotes tumor metastasis [92]. Previous studies have found that tumor-derived VEGF-A, VEGF-C, and VEGF-D induce lymphangiogenesis in the premetastatic microenvironment, further enhancing immunosuppressive responses and promoting tumor invasion and metastasis [10,93,94]. Recently, the research report found that tumor-derived exosomes facilitate tumor migration by promoting lymphatic PD-L1 upregulation and lymphangiogenesis, which induces immune escape in tumor cells [95]. Recently, a study has demonstrated that lymphatic network reformulation in the sentinel lymph nodes (SLNs) is engaged in the establishment of PMN (Table 1). CRC-derived exosomes form favorable conditions for CRC lymph node metastasis by metastasizing IRF-2 to F4/80+ macrophages and further inducing macrophages to highly express VEGF-C, which promotes endothelial cell proliferation and lymphangiogenesis, thereby participating in lymphatic network reconstruction in the PMN [75]. However, it remains unclear whether IRF-2 promotes liver metastasis of CRC through the formation of microecology before lymphatic vascular metastasis or changes in the microenvironment before liver metastasis. Further studies are required to investigate the inhibition of lymphangiogenesis as a potential treatment or preventative measure for tumor metastasis.

4.5. Organotropism

The metastasis of tumors is not random but is under the control of a series of cells and molecules, showing a tendency to colonize and metastasize to specific organs [96]. For example, colorectal cancer is prone to liver metastasis; and breast cancer has a high propensity for bone, hepatic and pulmonary metastases; in addition, melanoma and cancers originating in the colon, kidney, bladder, breast, neck and head easily cause lung metastasis [97].

Initially, the study of organotropism focused on the inherent characteristic role of cancer cells. An example is the direct receptor–ligand interaction between tumor cells and the distal microenvironment [98]. Recently, investigation has found that this property is related to exosome integrin-mediated PMN (Table 1) [98,99]. As is well known, integrins regulate cell attachment, spread, migration, and tumor invasion [100,76]. Exosomes secreted by organotropic breast tumor cell lines (MDA-MB-231) and pancreatic tumor cells (BxPC-3 and HPAF-II) have been labeled with near-infrared (NIR) or red fluorescent labeling and injected into mice; after 24 h, the specific uptake of exosomes into the lungs and liver of mice is detected, suggesting that exosomes are related to the organ specificity of tumor metastasis. In addition, exosomal integrin α_6 β_4 and α_6 β_1 are linked to pulmonary metastasis, while exosomal integrin $\alpha_v\beta_5$ specifically binds to Kupffer cells and mediates liver metastases. In clinical trials, ELISA detection has demonstrated that the content of exosomal ITGα_v in cancer patients with liver metastases is significantly increased compared with that in cancer patients without metastasis or lung metastasis [99].

Previous reports have demonstrated that $\alpha_v\beta_6$ is strongly expressed in colorectal cancer cells, creating a microenvironment suitable for CRC progression, which increases CRC invasion and metastasis [101]. By establishing liver colonization models (inject WiDr cells straight into the hepatic as they do not metastasize) and liver metastasis models (intrasplenic injection of HT29 cell lines with metastatic potential) in nude mice, recent research has demonstrated that liver metastasis accounts for 55% of mice injected with WiDr mock transfection agent expressing $\alpha_v\beta_6$ and that liver metastasis occurs in mice injected with intrasplenomegaly HT29 mock

transfection agent in up to 90% of cases; conversely, no visible hepatic metastatic nodules are observed in mice injected with anti-β6 WiDr and HT29 mock transfectants. The above data indicate that αvβ6 may promote CRC colonization, metastasis, and survival in the liver. Previous in vitro studies have demonstrated that αvβ6 promotes high expression of matrix metalloproteinase 9 (MMP-9), which facilitates the invasion and metastasis of CRCs by degrading the extracellular matrix. In summary, exosome surface-specific integrins determine which organ takes up exosomes and preferentially forms a premetastatic microenvironment in that organ [76]. In summary, exosomal integrins promote the formation of PMNs, which creates conditions for tumor metastasis, providing a research basis for the organ specificity of tumor metastasis. In addition, exosomal integrins may be used as a biological marker to predict tumor metastasis in the clinic. However, research on the relationship of other substances in exosomes with organ specificity and their clinical application is unclear, and further research is needed.

4.6. *Reprogramming*

The formation of the PMN is inseparable from metabolic reprogramming, matrix reprogramming, and gene reprogramming [102, 103]. CRC cells exhibit a particular metabolic reprogramming process during hepatic metastasis. Metabolic reprogramming is one of the basic characteristics of tumor cells (Table 1). [104]. Studies have shown that exosomes can interact with stromal cells and non-tumor cells in the PMN and cause metabolic reprogramming of recipient cells [88]. CAFs play a vital role in metabolic reprogramming [105]. A previous study has reported that serum exosomal HSPC111 expression levels in patients with liver metastases of CRC are higher than those in patients without metastases. CRC-derived exosomal HSPC111 promotes the activation of CAFs and phosphorylates ACLY, affecting the lipid metabolism of CAFs by upregulating the level of acetyl-CoA. Too much acetyl-CoA promotes the acetylation of H3K27 in CAFs and overexpression of CXCL5; CXCL5 acts on CXCR2, promoting increased secretion of CRC exosomal HSPC111. The above results indicate that CRC exosomal HSPC111 promotes the establishment of PMNs by reprogramming the lipid metabolism of CAFs, which promotes CRC liver metastasis [77]. Rai et al. found that exosomes secreted by primary and metastatic CRCs transform and activate quiescent fibroblasts that exhibit heterogeneity, which may be due to the exosomes secreted at different cancer stages have different protein profiles that induce CAFs to reprogram. Fibroblasts activated by primary CRC-derived exosomes highly express cell proliferation- and angiogenesis-related proteins (Rab10a and NDRG1). However, fibroblasts activated by metastatic CRC cell-derived exosomes highly express invasion-related proteins, including extracellular matrix disassembly proteins (MMP11, ADAM10, and EMMPRIN) and cytoskeletal reorganization proteins (MYO1B and PDML1). In summary, exosomes enhance CRC

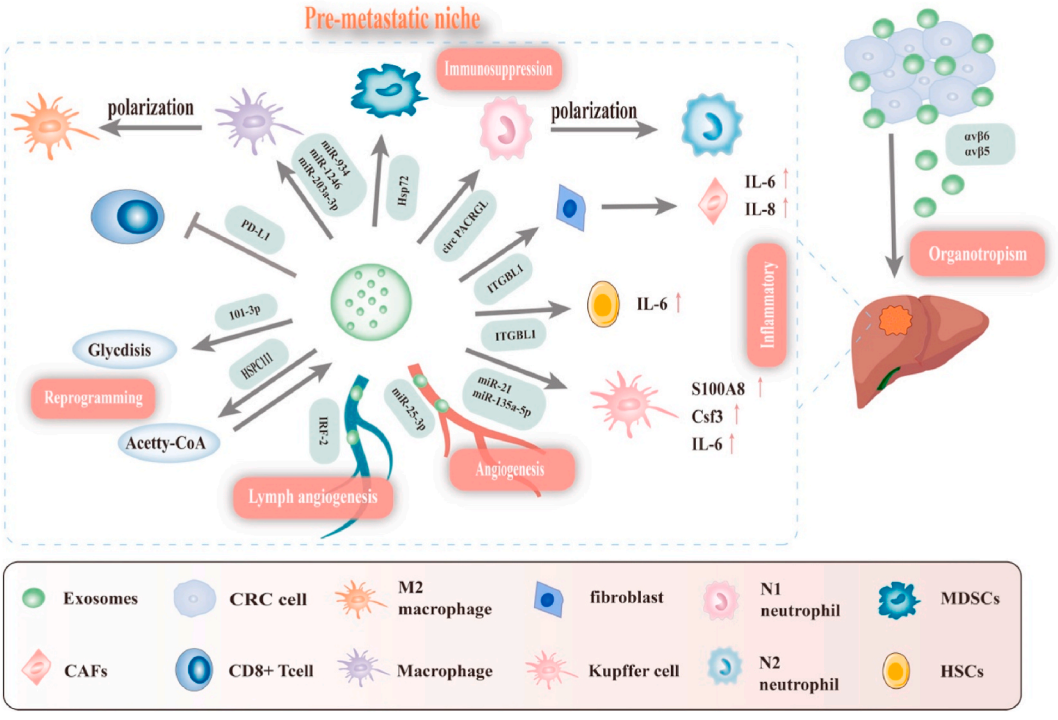

Fig. 2. Schematic showing the roles of exosomes in colorectal cancer premetastatic niches. Exosomes contribute to PMN formation through multiple mechanisms, including immunosuppression by recruiting MDSCs, facilitating TAM polarization, facilitating TAN polarization, inhibiting $CD8^+$ T cell activation, and inhibiting the inflammatory microenvironment, by activating CAFs and Kupffer cells to release inflammatory mediators as well as by activating angiogenesis, lymph angiogenesis, organ-specific metastasis, and metabolic reprogramming. The arrows represent activation, whereas bar-headed lines represent inhibition. CRC, colorectal cancer; CAFs, cancer-associated fibroblasts; MDSCs, myeloid-derived suppressor cells; TAM, tumor-associated macrophage; TAN, tumor-associated neutrophil; HSC, hepatic stellate cell.

aggressiveness and metastatic capacity by reprogramming CAF amino acid metabolism [78]. A previous study has found that exosomal 101-3p is strongly expressed in CRC patients and is positively correlated with glycolysis. HIPK3 is the downstream target of 101-3p, which reduces the expression of mitochondrial ADVC1 by targeting HIPK3, and ADVCI suppression reduces the production of mitochondrial reactive oxygen species (ROS), which weakens aerobic respiration and enhances glycolysis, thereby enhancing the metastatic ability of colorectal cancer [79]. Further research is needed to understand the role of exosomes in the matrix and gene reprogramming in the PMN of colorectal cancer.

5. Results

Before exploring the results of the mechanism of microenvironment development before liver metastasis in colorectal cancer, it is important to understand the complexity and multi-step character of this process. This chapter will present our findings in detail, including how exosomes play a key role in the multiple processes of EMT, invasion ability acquisition, and tumor migration in colorectal cancer cells. We will also explore how exosomes regulate the liver microenvironment, promoting the colonization of tumor cells in the liver and the development of metastases. In addition, our results also reveal the potential role of certain exosomes in inhibiting colorectal cancer progression, which provides new ideas for the treatment and monitoring of colorectal cancer prognosis.

The mechanism of development of the pre-liver metastatic microenvironment in colorectal cancer is a multistep, multilink, and multifactorial process (Fig. 2). The mechanism of PMN formation is currently being extensively studied. Exosomes play a key function in cancer progression. Under the action of exosomes, CRC cells undergo EMT and acquire invasion ability, which makes CRC cell transfer the first step. In the PMN, exosomes released from CRC cells are involved in multiple processes of tumor migration, including upregulation of inflammatory factors, organ-specific metastasis, evasion of immune monitoring, tumor angiogenesis, lymphangiogenesis, and metabolic reprogramming, which regulates the liver microenvironment and is conducive to CRC cell colonization and development of metastatic lesions in the liver. In addition, certain exosomes also inhibit CRC progression, suggesting that they have a potential role in treating and monitoring CRC prognosis. For example, miR-140-3p represses CRC progression and transfer by tracking BCL9 and BCL2, and targeting the miR-140-3p-BCL9/BCL2 axis is probably considered as a therapy strategy for CRC [106]. miR-375, miR-125b-5p, and miR-185-5p have also been reported as tumor suppressors that prevent CRC cell progression and metastasis [107,108]. A previous study has reported that the expression level of exosomal miR-122 in healthy people, CRC patients without metastasis, and CRC liver metastasis patients varies and that the expression level of miR-122 is strongly associated with the poor prognosis of CRC patients. Thus, miR-122 may be a specific diagnostic sign and prognostic indicator for patients with CRC liver metastases [109].

6. Future perspectives

The field of liver PMN research is still in its infancy. Nevertheless, the future of its clinical application looks bright. The first exosome-based liquid biopsy technology became commercially available in the United States in 2016 [110]. It symbolizes a step towards maturity of the emerging science of exosome biology. Currently, tissue biopsy remains the gold standard and the first-line clinical method for cancer identification [40,111]. Liquid biopsy, as a non-invasive, reproducible method, is expected to be a viable alternative to tissue biopsy. In recent years, with the intensive development of liquid biopsy technology, exosomes have great potential for clinical utility. They are anticipated to become diagnostic and prognostic biomarkers. Exosomes with microRNA-23b signature have shown promise as prognostic biomarkers for CRC patients in different phases. Studies have shown that microRNA-23b levels increase from early to metastatic phases. During this time, PMN is bound to evolve [112]. Therefore, they can be indirectly considered as biomarkers of PMN. However, more research is needed to establish biomarkers that directly indicate PMN formation.

In addition, PMN signaling pathways are regulated by exosomes, which may provide novel pathway to inhibit cancer metastasis. Exosomes can be thought of as therapeutic targets for CRC liver metastasis [40]. Studies have demonstrated that treatments targeting exosomal miR-21 and MIF can block exosome-derived hepatic metastases and prevent the formation of hepatic PMN [69,113]. Currently, while most research on PMN targeting has concentrated on the lung, the approaches used provide ideas for future research on liver PMN. One study found that injection of siS100A4-containing exosomes into mice after primary breast cancer resection reduced the occurrence of lung metastases [114]. Based on our current comprehension of the function of exosome integrins in inducing tumor organotropism, we believe that exploring the targeting of this process has potential therapeutic implications. As mentioned above, exosome integrins αvβ5 and αvβ6 are associated with liver-specific uptake and targeting them may prevent metastasis in high-risk patients.

Exosomes have outstanding tissue/cell penetration capacity , low immunogenicity and innate stability. These unique properties provide them with an advanced platform in cancer drug delivery. However, there is currently little information on the involvement of exosomes in the treatment of liver metastatic disease. The isolation and purification efficiency of exosomes is low, and the culture cost is high. This is extremely challenging for large-scale production and storage of exosomes. At present, microfluidics-based fabrication provides a viable strategy for regulated and scalable exosome production [115]. In addition, several researchers are working to optimize yield by manipulating growing conditions and gene expressions [116].

Even though exosomes have a promising application in PMN, there are still some challenges that need to be addressed urgently. First, future work should focus on how to more effectively utilize the potential of exosomes in cancer therapy, especially in the early detection and targeted therapy of colorectal cancer. Second, with the development of emerging technologies, such as advanced bioinformatics tools and nanotechnology, we have the opportunity to gain a deeper understanding of the molecular mechanisms and biological functions of exosomes. In addition, many key questions remain to be answered, such as how exosomes selectively interact

with specific cell populations and what their common and unique roles are in different cancer types. In-depth study of these questions will not only help us better understand tumor biology, but may also reveal new therapeutic strategies. Finally, PMN are spatiotemporally specific. Identifying PMN in mouse in vivo models remains difficult, let alone humans. Therefore, how to accurately identify PMN will continue to be a challenge in the future.

7. Conclusion

Before discussing the role of exosomes in the pre-metastasis microenvironment and drawing conclusions, we must emphasize the breadth and complexity of exosomes research. The in-depth study of exosomes in the pre-metastatic microenvironment provides a new research idea for monitoring, prevention, treatment and drug-resistant tumor metastasis, and provides a new hope for improving the survival rate of patients with tumor metastasis. However, the diversity and complex composition of exosomes make it difficult to translate them into clinical applications, suggesting the need for further research. Therefore, additional research and understanding of the mechanism of exosome formation in the pre-metastatic microenvironment may enable exosomes to be safely, effectively, and reliably used in clinical applications to prevent and intervene in colorectal cancer liver metastasis.

Ethics statement

Review and approval by an ethics committee was not needed for this study because this was a literature review, and no applicants/patients were enrolled. For the same reason, informed consent was not required.

Data availability statement

Data associated with the study has not been deposited into a publicly available repository and no additional data was used for the research described in the review article.

CRediT authorship contribution statement

Guifei Si: Writing – review & editing, Writing – original draft, Visualization, Software, Resources, Conceptualization. **Xuemei Chen:** Writing – review & editing, Visualization, Supervision, Resources. **Yuquan Li:** Writing – review & editing, Visualization, Supervision. **Xuemin Yuan:** Writing – review & editing, Visualization, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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