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Review Article

Exosomal non-coding RNAs: Blueprint in colorectal cancer metastasis and therapeutic targets

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ABSTRACT

Colorectal cancer (CRC) is ranked as the world's third-most prevalent cancer, and metastatic CRC considerably increases cancer-related fatalities globally. A number of complex mechanisms that are strictly controlled at the molecular level are involved in metastasis, which is the primary reason for death in people with CRC. Recently, it has become clear that exosomes, which are small extracellular vesicles released by non-tumorous and tumorigenic cells, play a critical role as communication mediators among tumor microenvironment (TME). To facilitate communication between the TME and cancer cells, non-coding RNAs (ncRNAs) play a crucial role and are recognized as potent regulators of gene expression and cellular processes, such as metastasis and drug resistance. NcRNAs are now recognized as potent regulators of gene expression and many hallmarks of cancer, including metastasis. Exosomal ncRNAs, like miRNAs, circRNAs, and lncRNAs, have been demonstrated to influence a number of cellular mechanisms that contribute to CRC metastasis. However, the molecular mechanisms that link exosomal ncRNAs with CRC metastasis are not well understood. This review highlights the essential roles that exosomal ncRNAs play in the progression of CRC metastatic disease and explores the therapeutic choices that are open to patients who have CRC metastases. However, exosomal ncRNA treatment strategy development is still in its early phases; consequently, additional investigation is required to improve delivery methods and find novel therapeutic targets as well as confirm the effectiveness and safety of these therapies in preclinical and clinical contexts.

1. Introduction

Colorectal cancer (CRC) is a major cancer-causing fatality and a serious global health concern [1]. The key factor in patient death from CRC occurs when cells expand metastatically to other organs [2]. The process of metastasis is intricate and multifaceted, involving the dissemination of cancerous cells, their survival in the bloodstream, extravasation at distant sites, and the development of secondary tumors [3]. Tiny extracellular vesicles, termed exosomes, have received a lot of interest recently due to the fact that they make intercellular communication easier and accelerate the development of cancer [4].

Exosomes and/or small extracellular vesicles (EV) are 50–150 nm-sized bilayer lipid vesicles that are propelled by endosomal processes, whereas micro-vesicles (MVs) are produced in cells under stress conditions by membrane blebbing and whose diameter ranges from 50 to 500 nm and sometimes up to 1 μm [5]. They are secreted by most cancerous

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and non-cancerous cells and include a wide variety of bioactive chemicals [6,7]. Of particular interest are non-coding RNAs (ncRNAs), such as microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), which perform significant regulatory functions in several biological pathways, including carcinogenesis, signaling pathways, and gene expression [8].

Exosomal ncRNAs have become key participants in the setting of CRC metastasis, altering the functions of cells and encouraging metastatic dissemination [9]. They have the ability to travel from primary tumor cells to distant places, where they are absorbed by recipient cells and have their intended effects [10]. These effects include enhancing angiogenesis [11], triggering the epithelial-mesenchymal transition (EMT) [12], controlling immunological responses [13], and establishing a favorable pre-metastatic environment for later colonization [14].

NcRNAs found in exosomes may function as early-stage diagnostic biomarkers for the early detection of metastatic CRC by offering non-invasive and precise indicators of disease progression [8]. It holds considerable promise in order to create brand-new therapeutic targets and diagnostic biomarkers to identify individual ncRNAs involved in CRC metastasis and characterize their downstream targets and signaling cascades [15]. Exosomal ncRNA functions in CRC metastases are important to understand since they have a big impact on treatment and diagnosis.

The purpose of this review is to investigate the complex interaction among exosomal ncRNAs and CRC metastasis, clarifying their functions as important contributors to the design of metastatic processes. Although it aims to shed light on how particular ncRNAs are encapsulated in exosomes and discharged into the extracellular fluid (ECF) by discussing exosome biogenesis and cargo selection mechanisms. Furthermore, elucidate the therapeutic potential of exosomal ncRNAs as desirable targets for the creation of novel therapeutic approaches. However, the creation of exosomal ncRNA therapeutic strategies is still in its early phases and it needs deep understanding.

2. Biogenesis of exosomes

The multistep intracellular process of exosome synthesis involves a number of unique steps [16]. Early endosomes are created during the biogenesis process from the inward budding of the plasma membrane [17]. The early endosomes then go through a maturation process in which they pick up different proteins and lipids, giving rise to late endosomes [18]. Multivesicular bodies (MVBs), which are defined by having intraluminal vesicles (ILVs) within their lumen, are formed when late endosomes continue to mature [19]. The machinery known as the endosomal sorting complex required for transport (ESCRT) is responsible for the endosomal membrane's inward budding, which results in the formation of the ILVs [20]. Numerous protein complexes, including ESCRT-0, ESCRT-I, ESCRT-II, and ESCRT-III, in addition to related proteins like VPS, Alix, TSG 101, and CHMP2B proteins, make up the ESCRT machinery [21,22]. Proteins, nucleic acids like DNA, mRNA, and ncRNAs, and lipids are only a few of the unique cargo molecules that are specifically sorted into ILVs during their creation [19,23–25]. Several systems mediate cargo sorting, such as ESCRT-independent systems, ESCRT-dependent recognition of ubiquitinated cargo, and interactions with RBPs [26,27]. MVBs can proceed in any of two ways: either via fusion with the plasma membrane or lysosomal disintegration to release exosomes [28]. The Rab GTPase protein family controls MVB fate by directing MVB trafficking along predetermined cellular routes [29]. In contrast to MVBs that are destined for exosome release, Rab11 and Rab35 are linked to MVBs that are trafficked toward lysosomes for breakdown by Rab7 and Rab27 [24,30]. Exosomes are produced from ILVs and released into the extracellular environment when MVBs fuse with the plasma membrane [31]. Multiple proteins, notably SNARE proteins, which facilitate the membrane fusion process, interact intricately to control the fusion process [32]. Exosomes that have been released can be absorbed by recipient cells through endocytosis or direct membrane fusion [33] (Fig. 1). This well-controlled process makes sure that cargo molecules are packaged into exosomes in a certain manner, enabling communication and their participation in numerous pathological and physiological activities.

3. Components of exosome

Exosomes are made up of a complex variety of biomolecules, such as carbohydrates, lipids, proteins, and nucleic acids. The following are exosomes' primary constituents.

3.1. Exosomal proteins

Proteins found inside exosomes are known as "exosomal proteins." They can develop during their biogenesis either directly from the parent cell or by being carefully packaged into exosomes [34]. In accordance with the type of cell, the condition of the cell, and the external environment, exosome protein composition can vary [35]. Many studies have discovered and described a vast variety of proteins connected to exosomes produced by various cell types.

Exosomes contain several different types of proteins with various biological functions. For instance, heat shock proteins (HSP) are a class of proteins that support protein folding and the cellular stress response [36]. There are different types of HSP in exosomes, including HSP27, HSP60, HSC70, and HSP90 [37], while the most important exosomal HSPs are HSP70 and HSP90 [38]. Chaperone proteins like HSP70 are crucial for protein folding, quality control, and cellular homeostasis. They are also implicated in cellular stress responses [39]. Although the folding, stability, and activation of other client proteins are all made easier by the presence of the highly conserved molecular chaperone HSP90 [40,41]. Similarly, tetraspanins, which are membrane-integral proteins, are frequently utilized as exosomal markers [42]. Among them, CD63, CD9, CD82, and CD81 are the most important membrane-integral proteins [24]. Likewise, annexins have a role in membrane-related activities such as vesicle trafficking and membrane fusion. Annexins 1 (ANXA1) and 2 (ANXA2) have been found in exosomes [43,44]. It has been discovered that the protein ANXA1 has a variety of functions in exosomes, such as reducing inflammation [45], immune control [46], regulation of apoptosis [46], repair and regeneration of tissues [47], and tumor development and metastasis [48]. While ANXA2 has essential functions in cell-to-cell communication [49], remodeling of membranes and extracellular matrix [50], sorting cargo [23], and biogenesis of exosomes [51]. Moreover, exosomes can include adhesion molecules like integrins and selectins, which are involved in interactions between cells and the matrix [52,53]. Additionally, exosomes also include proteins termed "antigen-presenting molecules." Exosomes may include MHC class I and class II molecules produced by antigen-presenting cells (APCs) like macrophages, B cells, and dendritic cells [54,55]. Furthermore, exosomes have been found to include several different metabolic and protease enzymes, such as matrix metalloproteinases (MMPs) [56], proteasome subunits [57], and glycolytic enzymes (like aldolase and enolase) [58]. Although they can contain enzymes that are part of biological pathways, including receptor tyrosine kinases (like EGFR) [52], and elements of the Notch and Wnt pathways [59]. Exosomes also include RNA-binding proteins and DNA-binding proteins, which implies that they might contribute to the transfer of RNA and DNA between cells [60].

Overall, exosomal proteins are currently the subject of intense research to more fully comprehend their functions in diverse biological processes and investigate their capabilities as diagnostic and therapeutic targets.

3.1.1. Exosomal proteins secreted from non-mutant KRAS CRC cells effect on metastasis

Another exosomal protein associated with mCRC is calcium-dependent activator protein for secretion 1 (CAPS1), in which

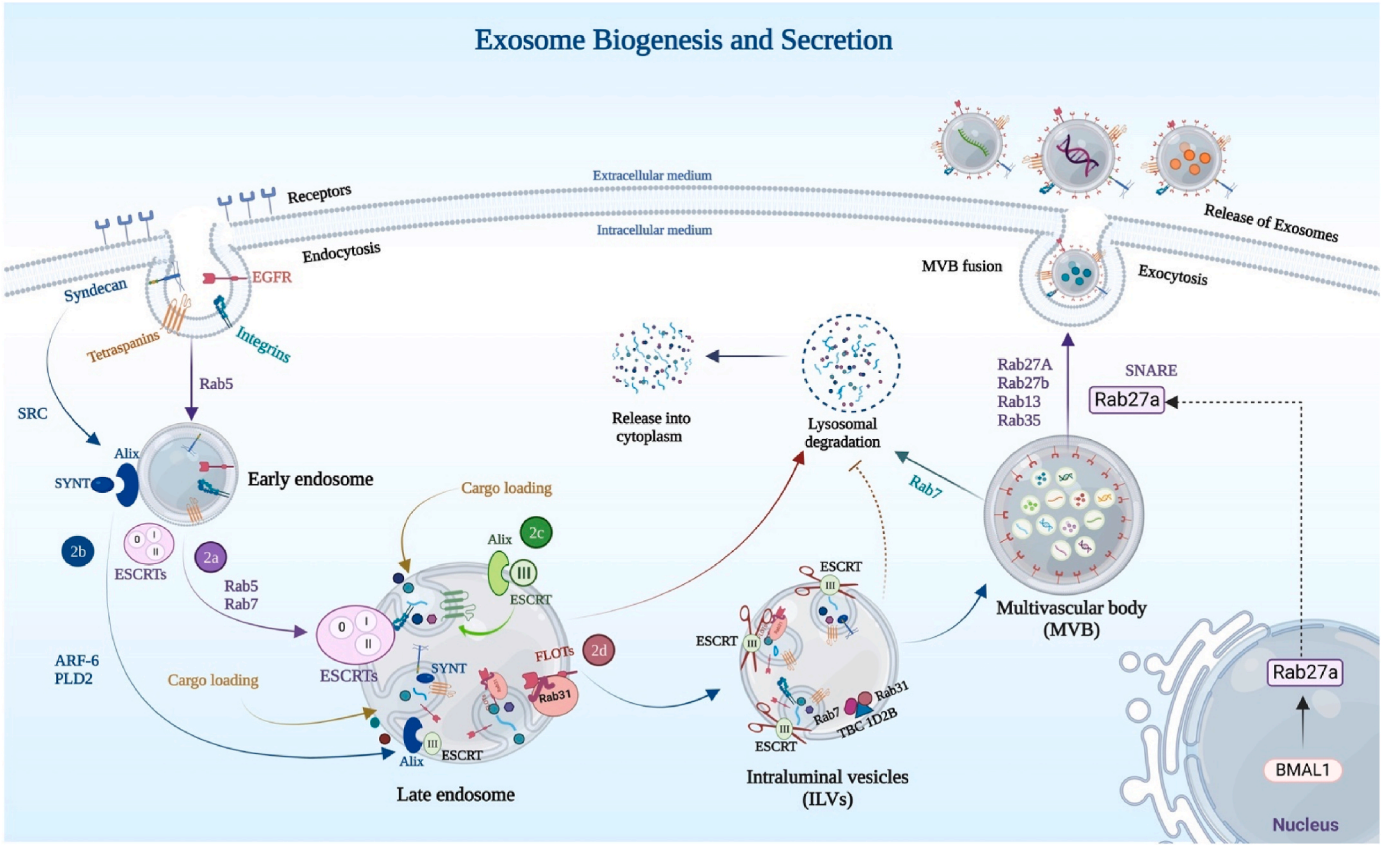

Fig. 1. Pathways involved in exosome biogenesis. Exosome biogenesis concludes several steps: [1] Endocytosis, the process of the plasma membrane's inward budding; [2] early endosome formation resulting from the inward budding of the plasma membrane; [3] late endosome: in this process, the early endosome membrane buds inward to start the process of cargo loading; [4] the ILV follows the previous process where cargo loading and scission of the ILVs occur; [5] the MVB contains all synthesized exosomes and will undergo two possible processes: (6a) where the plasma membrane is agitated by the MVB to secrete its exosomal cargo into the extracellular environment; (6b) where the MVB undergoes-lysosomal degradation from the step of the early endosome up to the formation of the MVB, several pathways are involved in the process of cargo sorting into late endosomes; namely, (2a) represents the classical ESCRT machinery pathway, where ubiquitinated cargo proteins rely on early functioning ESCRTs (ESCRT-I, II, and III) to be loaded into ILV, and ESCRT-III is involved in the scission of these ILV to form MVB. (2b) Represents the Syndecan-Syntenin-Alix pathway with its regulators, SRC and ARF6/PLD2. (2c) Represents the Alix-ESCRT–III–tetraspanin pathway. The 2a and 2b pathways depend on Alix's unique feature to deliver un ubiquitinated cargoes directly to ESCRT-III, escaping the need for early ESRTs. (2d) Represents an ESCRT-independent pathway mediated by Rab31 activating the EGFR receptor to later form a complex of Rab31-EGFR-FLOT and drive exosome biogenesis independently from all ESCRT machinery. Rab31 then conjugates with TBC1D2B to inactivate Rab7 and prevent its lysosomal degradation.

exosomes produced from CRC cells overexpressing CAPS1 increased metastasis of non-migrating normal colonic epithelial cells, possibly mediated by downregulation of exosomal bone morphogenic protein (BMP4). According to liquid chromatography-mass spectrometry analysis, bioinformatic analysis, and Western blot analysis, CAPS1 overexpression can modify exosomal protein profiling, sharing 437 exosomal proteins in common while 138 CRC-exosomes and 135 proteins for control exosomes differed [61].

Exosomal ADAM 17 (disintegrin and metalloproteinase 17), a membrane protein, was found to be overexpressed in mCRC, specifically being involved in liver metastasis both in vivo and in vitro by means of dissociating *E*-cadherin, consequently enhancing tumor cell migration. These results were further supported by increasing the levels of the mesenchymal markers snail, vimentin, and *N*-cadherin. Additionally, it showed an elevated level in the serum of mCRC patients, making it a possible candidate as a metastasis-based blood-based biomarker [62]. Furthermore, another exosomal protein found to be correlated with mCRC was frizzled proteins (FZD). This group of G protein receptors functions as receptors for the Wnt signaling pathway, where they activate the mitogen-activated protein kinase (MAPK) axis. More specifically, FZD10 was shown to be upregulated in plasma-driven exosomes and patient tissues, with higher increments being associated with advanced TNM stages of CRC. Exosomal-FZD10 can activate the tissue antigen for cell proliferation, Ki-67, possibly by activating both conventional and unconventional Wnt pathways and subsequent MAPK3 (*p*-ERK1/2 and ERK1/2) activation [63]. Another assay also highlighted the effect of FZD10 on CRC metastasis, in which exosomes from the CaCo-2 and SW620 cell lines of CRC were loaded with FZD10, hence activating EMT. The exosomes produced by the metastatic SW620 cell line contained significantly greater amounts of FZD10 and C-Myc in comparison to exosomes from the non-metastatic CaCo-2 cell line, thus resulting in more profound EMT activation in healthy colonic epithelial cells, as evidenced by an increment in mesenchymal markers vimentin, β-catenin, and Slug/Snail [64] (Fig. 2a).

3.1.2. Exosomal proteins secreted from KRAS mutant CRC cells effect on metastasis

Ras-pathway-related proteins, including EGFR, Rho, Rac, and Ral GTPases, have a significant contribution to exosome biogenesis, and mutant KRAS has been detected in many cancer-related exosomes [65]. Mutant KRAS status during cancer development has a critical effect on altering the proteomic composition of exosomes and consequently on recipient cells. Exosomes driven from colon cancer cells with mutant KRAS were found to be high in oncogenic proteins, such as SRC family kinases, EGFR, KRAS, and integrins [66]. EGFR signaling was found to trigger the secretion of MV from the cell's plasma membrane via

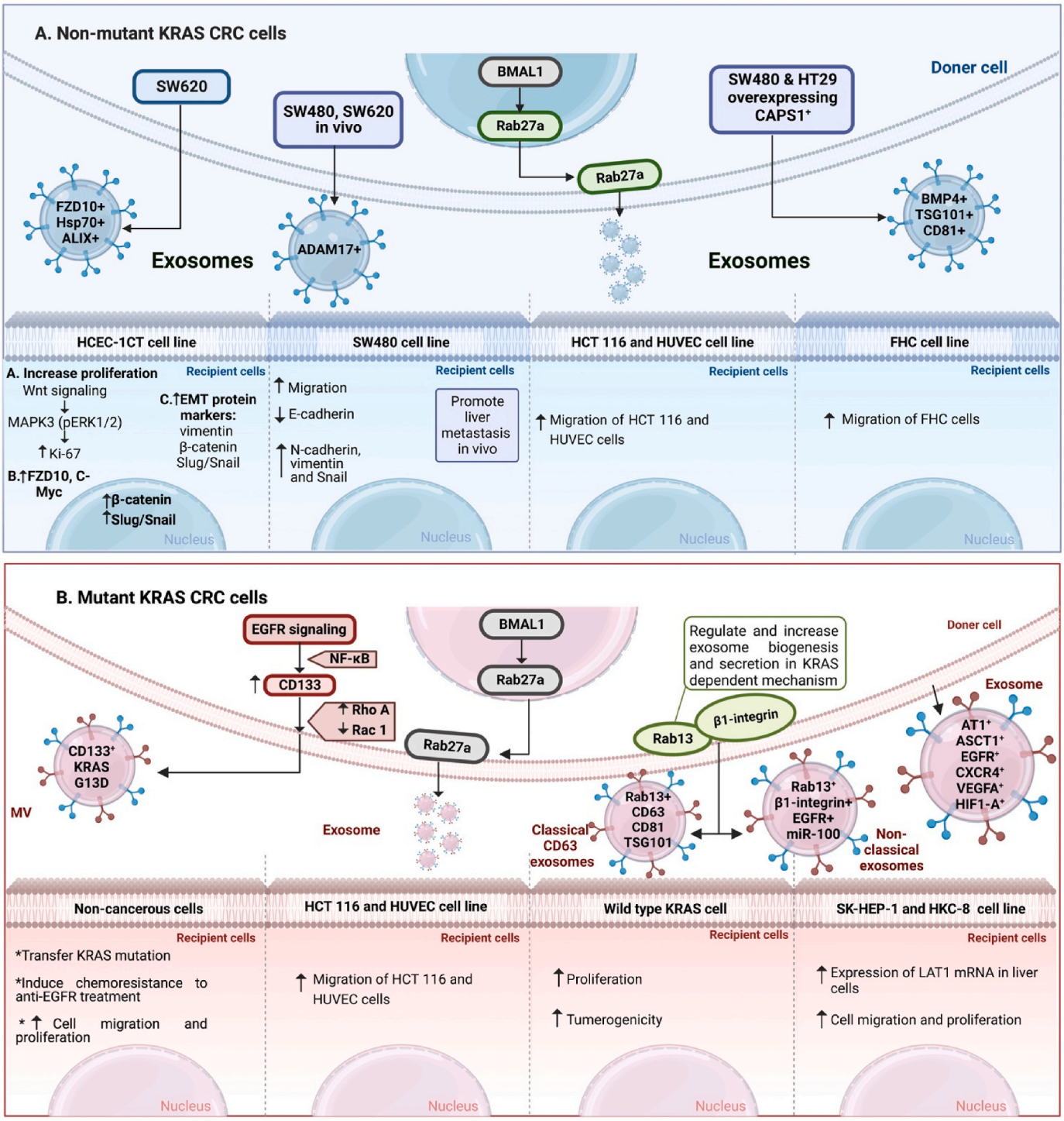

Fig. 2. Mechanisms by which exosomal proteins secreted from CRC cells promotes metastasis of CRC in recipient cells. (A) Exosomal secretion from non-mutated KRAS CRC cells.

activation of CD133 and NF-κB expression [67]. A CSC marker, CD133, is involved in exosome biogenesis by regulating downstream Ras small GTPase proteins Rac1 and RhoA [67,68]. CD133+ MVs secreted from HCT116 cell lines acted as cell-to-cell communicators, delivering KRAS mutants to adjacent non-cancerous cells, which consequently activated oncogenic KRAS signaling in the cells, enhanced metastasis of CRC by increasing neighboring cell motility, and participated in inducing chemoresistance to anti-EGFR drugs by enhancing cellular proliferation and motility [67]. Additionally, patients with mCRC exhibited a significantly high concentration of CD133+ and EPCAM + extracellular vesicles in their blood [69].

Moreover, Almeida and his collaborators found that the mCRC cell line HCT-116 produced exosomes loaded with the amino acid transporters LAT1 and ASCT mRNA that could be taken up by several different cell types, including the hepatocellular carcinoma cell line SK-HEP1. These exosomes were also loaded with VEGFA, HIF1-A, EGFR, and CXCR4 mRNAs. The phenotypic effect of these exosomes on the SK_HEP1 cell line included an increment in protein expression of LAT1

mRNA and enhancement of cell migration and proliferation [70]. Rab 13 functions in KRAS mutant CRC cells as both a cargo protein and a promoter of exosome synthesis and secretion, in which KRAS activation drives Rab-13-dependent exosome biogenesis [71]. Rab 13 regulates the release of classical exosome biomarkers CD63, TSG101, CD81, and a non-classical moiety β1-integrin. Collectively, mutant KRAS cancer cells secrete Rab13+, β1-integrin+, and EGFR + exosomes [71].

Lastly, exosome uptake was found to be dependent on the kind of receiver cell instead of the producing cell in CRC, and exosomal uptake by the mCRC cell line HCT-116 was modulated by clathrin-dependent endocytosis rather than caveolae-dependent endocytosis. Meanwhile, in the COLO205 cell line, exosome uptake depended on both mechanisms [72] (Fig. 2b).

3.2. Exosomal lipids

Lipids, which are abundant in exosomes, are essential to their biosynthesis, stability, and functionality [73]. Sphingolipids and/or sphingomyelin, lipid rafts, phospholipids, fatty acids, lipid metabolites, and cholesterol comprise major lipid subclasses of the cell membrane and eventually the exosomal membrane [74,75]. The type and physiological status of the producer cell and the destined function of the exosome govern the relative lipid abundance in exosomes [76]. One of the essential lipids in the creation and release of exosomes is the sphingolipid ceramide, which exists in abundance in exosomes compared to their producer cell membrane [77]. Lipid membranes are anisotropically arranged in superstructures called lipid rafts [78]. Ceramides are arranged as ceramide-rich platforms (CRP) and represent a type of lipid raft on the exosomal surface. Hence, exosomes can contain mobile rafts such as CRP, ceramide-associated proteins (CAP), and raft-associated proteins (RAF). Donor cells share these lipid rafts via exosomes, thereby activating the same pathways in recipient cells. These rafts play a critical role in activating pathways in cancer and metastasis [79].

Interestingly, exosomes from mCRC were found to be enriched with lipid rafts and components linked with lipid rafts (FLOT2, CAV1, FLOT1, and PROM1) [80]. These exosomal lipid rafts play a role in ESCRT-independent cargo loading into exosomes [51]. Moreover, another of the most prevalent lipids in exosomes are phospholipids, which are made up of a phosphate group, two fatty acids, and a glycerol backbone [81]. They establish the fundamental framework of the lipid bilayer that encloses the exosome's composition [82]. Phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol are typical phospholipids present in exosomes [13]. Furthermore, fatty acids, which make up the majority of lipids, are present in exosomes in diverse forms [83]. The physical characteristics of the exosomal membrane can be influenced by the makeup of fatty acids, which might be saturated or unsaturated [81]. Additionally, leukotrienes, prostaglandins, and lipoxins are key mediators of inflammation and cell signaling that can be transported by exosomes along with other lipid metabolites [84].

In CRC, exosomes made from the LIM1215 cell line had different levels of sphingolipids, glycerolipids, sterol lipids, and/or cholesterol, as well as the glycerophospholipid plasmalogen [85]. Similarly, a recent study using the multi-omic technique for exosomal analysis driven from both cell cultures and blood samples from people with CRC showed the diversity of proteomic, lipidomic, and metabolomic variables in comparison to their paired controls, of which 130 cell culture lipids and 56 serum lipids, 9 cell culture proteins and 13 serum proteins, and 37 cell culture and 31 serum metabolites were differentially and significantly expressed in CRC exosomes. Thereafter, a joint pathway analysis revealed three common joint pathways to change significantly in CRC both in exosomes generated from serum and in cell culture: the unsaturated fatty acid biosynthesis pathway for the production of aminoacyl-tRNA, phenylalanine-tyrosine, and tryptophan [86].

3.3. Exosomal non-coding RNA

Non-coding RNA molecules, or RNA molecules without protein coding but having crucial regulatory functions in cells, are present in exosomes in different forms [87]. These ncRNAs can be transmitted across cells while being contained in exosomes, changing the biological processes and gene expression of the receiving cells [88]. Exosomes function as essential transporters for all varieties of ncRNAs, and through them, they mediate nearly all cancer hallmarks that lead to CRC metastasis [7,89] (Fig. 3).

One prominent type of ncRNA found in exosomes is circRNA [90]. CircRNAs are one of the subclasses of ncRNAs, which are formed from the linear RNA molecule by a covalent bond between the 5′ and 3′ ends and produce a ring structure [88]. Exosomal circRNAs are thought to modulate cellular functions, act as sponges for miRNA, and control the expression of genes [91]. For instance, Yang et al. found that hypoxia-driven exosomal circ-133 promoted CRC metastasis through modulation of the miRNA-133a/GEF-H1/RhoA pathway upon delivery into normoxic tumor cells. Circ-133 downregulation could prevent metastasis in an in vivo model of xenografted mice with CRC, thereby representing a potential therapeutic target [92]. Similarly, exosomes containing circ-ABCC1 were discovered to be secreted by CD133+ CRC cells. Through Wnt/β-catenin pathway activation, these exosomes increased CRC cell stemness and metastasis [93]. Besides being metastasis promoters, exosomal circRNAs can also suppress metastasis. Zeng and his colleagues' most recent research on circFNDC3B clarified that exosomal circFNDC3B suppressed angiogenesis of CRC and metastasis through the circFNDC3B/miRNA-937–5p/TIMP3 axis, where circFNDC3B negatively targeted miRNA-937–5p [94].

Small RNA molecules known as miRNAs are another class of ncRNAs, which typically have a length of 22 nucleotides and have been found to be present in exosomes [95]. Exosomal miRNAs can be received by target cells, where they can influence the expression of genes and take part in several biological functions, such as development, immunological response, and metastasis [96,97]. For instance, Sun et al. discovered that, when compared to exosomes from the initial SW480 cells, exosomes from metastatic CRC SW620 cells boosted CRC cell invasion, motility, and EMT. Further, by focusing on *RASA1*, a potential inhibitor of RAS activity, we identified the shuttling of miR-335–5p exosomes as the fundamental regulatory mechanism promoting CRC cell motility, invasion, and EMT [98].

LncRNAs are another type of RNA molecule that is longer than 200 nt, has a restricted capacity for protein coding, and is also found in exosomes [99,100]. They have a variety of functions in chromatin remodeling, gene control, and cellular activities [101,102]. Exosomal lncRNAs are capable of being transported between cells and contribute to signaling and intercellular communication processes [103]. For instance, Xu et al. demonstrated that by sponging miRNA-26a/26b, exosomal MALAT1 encouraged the metastatic malignant behavior of CRC cells by controlling *FUT4* and activating PI3K/Akt/mTOR signaling [104]. Similarly, Fang et al. confirmed that exosomal lncRNA PCAT1 promotes tumor circulating cell-mediated CRC liver metastases by inhibiting the function of the miRNA-329–3p/Netrin-1-CD146 complex [105] (Table 1).

Small nuclear RNAs (snRNAs) [106], small nucleolar RNAs (snoRNAs) [107], and PIWI-interacting RNAs (piRNAs) [108], are additional ncRNAs that can be discovered in exosomes. In the RNA processing, modification, and genome stability processes, these ncRNA molecules play unique roles [107,108]. Their inclusion in exosomes increases the potential for them to be involved in RNA metabolism control and intercellular communication.

4. Exosomal ncRNA-mediated crosstalk between TME and PMN

Exosomal ncRNA is a key facilitator of the interaction between the premetastatic niche (PMN) and the tumor microenvironment (TME),

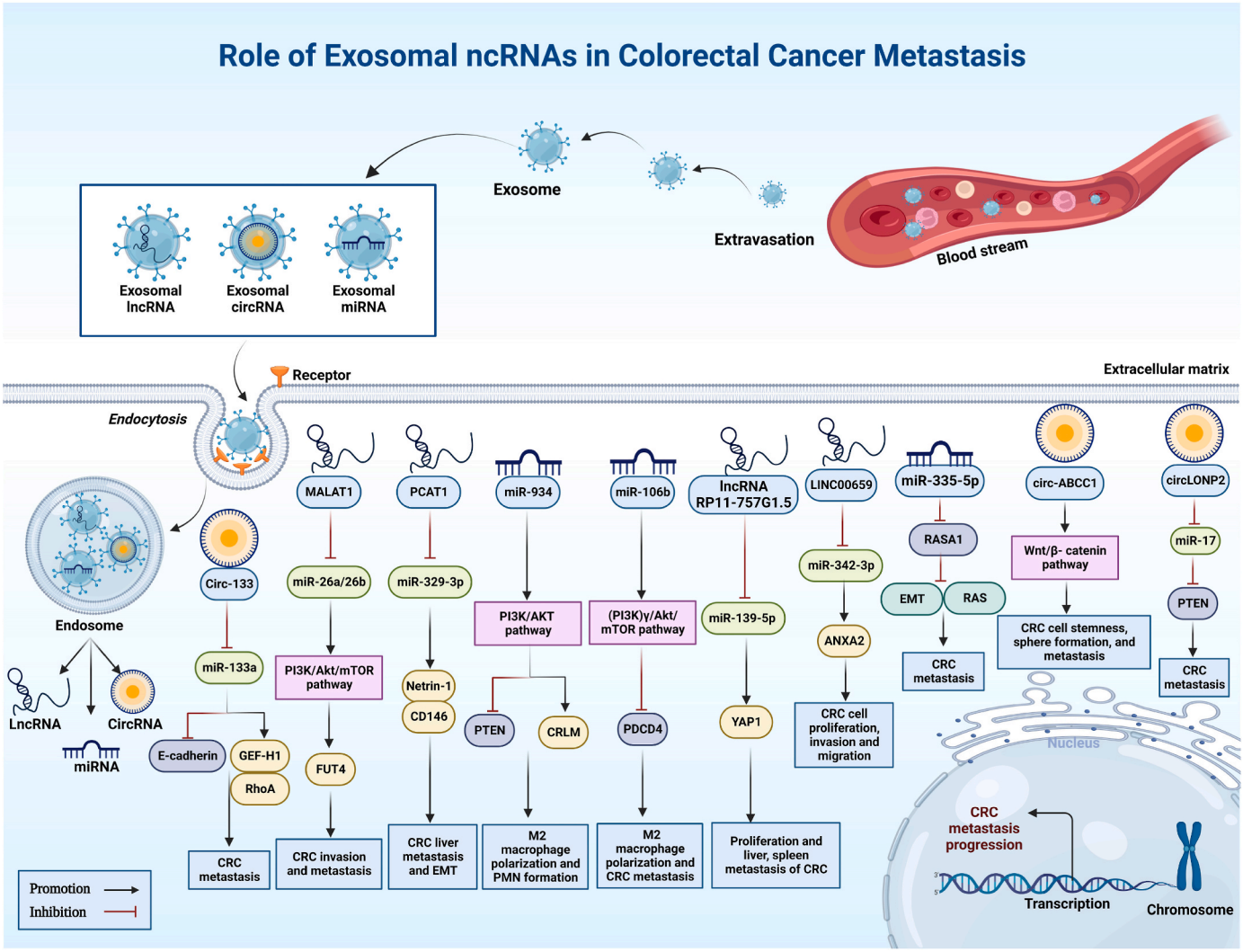

Fig. 3. An illustration demonstrates the involvement of ncRNAs and oncogenic signaling pathways in CRC metastasis. NcRNAs (such as miRNAs, circRNAs, and lncRNAs) may stimulate CRC metastasis, and survival of tumor cells by focusing on specific genes and sponging different kinds of microRNAs, including miRNA-133a, miRNA-26a/26b, miRNA-329–3p, miRNA-139–5p, miRNA-342–3p, and miRNA-17. NcRNA may regulate a number of crucial signaling pathways, acting as an oncogene and encouraging CRC spread, such as the PI3K/Akt/mTOR, PTEN/PI3K/AKT, and (PI3K) γ/Akt/mTOR pathways.

which aids in the spread of cancer [129]. The PMN is the favorable milieu in distant organs that encourages the mobility and survival of circulating tumor cells (CTCs) as well as the development of metastatic lesions [130]. Exosomes generated by tumor cells in the original tumor site and cells in the TME carry different kinds of ncRNAs [131]. These exosomal ncRNAs have the ability to go to distant places and affect PMN formation.

Exosomal miRNAs target particular genes and pathways in recipient cells, which has a substantial impact on regulating the PMN and TME [132]. For instance, Zeng et al. showed that exosomal miRNA-25–3p is important in the establishment of PMNs, which targets *KLF2* and *KLF4* to control the expression of *VEGFR2*, *ZO-1*, *occludin*, and *Claudin5* in endothelial cells, which in turn promotes vascular permeability and angiogenesis and could be exploited as a blood-based biomarker for CRC metastasis [133]. It is crucial to comprehend the specific ncRNA cargo and their functional consequences in this interaction in order to create targeted therapies to interfere with PMN synthesis and prevent cancer spread.

4.1. *Exosomal ncRNAs prepare TME for metastasis*

Exosomal ncRNAs may indeed help prepare the TME for metastasis, according to research [14]. The extracellular matrix components are present in the TME along with different cell types such as immune cells (including NK cells, tumor-associated macrophages, T and B lymphocytes, neutrophils, and dendritic cells) [134,135], stromal cells (such as endothelial cells, mesenchymal stem cells, stellate cells, fibroblasts, and adipocytes) [136], and blood vessel cells [137]. Non-cellular components of TME are exosomes and ECM (glycoprotein, collagen, fibronectin, elastin, and proteoglycan, among others) [138]. It is well established that it is essential for the spread of CRC because it offers a favorable environment for tumor cells to infiltrate nearby tissues, travel through the bloodstream or lymphatic vessels, and eventually form secondary tumors in other organs [139]. The stromal cells in the TME of CRC become involved in the ECM's renovation, creating immunosuppression and inflammation in the TME [140]. Exosomes, which are secreted locally and circulated, allow non-cancerous cells, including immune cells and stromal cells, to interact with cancer cells [141]. Similar to how cancerous cells communicate with non-tumorous cells in the TME, non-tumorous cells secrete exosomes in the TME that may control tumor growth [142].

Exosomal ncRNAs have a variety of potential effects on the tumor microenvironment [143]. They can be ingested by recipient cells in the microenvironment, where they can change how those cells behave and

Table 1
Exosomal ncRNAs play a role in the metastasis of CRC by controlling several signaling pathways that contribute to the alteration of several physiological functions.

Exosomal non-coding RNA	Expression	Cell Line	Animal Model	Type of Specimen	Pathways	Functions	Ref.
Circ-133	↑	HCT116, SW480	Nude mice	CRC tissues and paired adjacent noncancerous tissues	Circ-133/miRNA-133a/GEFH1/ RhoA, *E*-cadherin	Promotes cell migration.	[92]
Circ-ABCC1	↑	Caco2, HCT15	–	–	Wnt/β-catenin	Contributes to cell stemness, metastasis, and sphere formation.	[93]
CircFNDC3B	↓	LoVo, HCT116, SW480, SW620, HUVEC, 293T	–	CRC tumor tissue = 20 pairs	CircFNDC3B/ miRNA-937–5p/ TIMP3	Inhibits liver metastasis, angiogenesis, and CRC tumor growth.	[94]
LINC00659	↑	LoVo, SW48	–	Fresh CRC and adjacent normal tissues	LINC00659,miRNA-342–3p, ANXA2	Promotes CRC cell proliferation, invasion, migration, and EMT progression.	[109]
CircEIF3K	↑	HCT116, SW620, 293T	Nude mice	CRC patient data sets were downloaded (275 tumors and 349 normal tissues)	CircEIF3K/miRNA-214/PD-L1	Encourages tube formation, invasion, and proliferation.	[110]
CircPACRGL	↑	HCT116, SW480	Nude mice	Tumor tissues and recent plasma from CRC patients	CircPACRGL, miRNA-506–3p, miR-142–3p, TGF-β1	Encourages N1 to N2 neutrophil differentiation, migration, and invasion of CRC cells.	[111]
LncRNA RPPH1	↑	HCT8, HT29, SW620, 293T	Nude mice	CRC tissue = 61 pairs	TUBB3	Enhances CRC cells' migration, invasion, and EMT and triggers M2 macrophage polarization.	[112]
LncRNA SNHG10	↑	SW480, NK92-MI	–	CRC tissue = 30 pairs	INHBC/TGF-β	Suppresses the function of natural killer cells and induces EMT.	[113]
CircLONP2	↑	DLD-1, SW480, HCT116	Nude mice	CRC tissue samples	circLONP2/DGCR8, DDX1/miRNA-17, PTEN	Enhances invasion and metastasis.	[114]
B3GALT5-AS1	↓	NCM46, LoVo, HCT116, SW480, HT-29, SW620	Nude mice	- CC tissues = 64 pairs - Colon cancer liver metastasis tissue = 15 samples	B3GALT5-AS1/ miRNA-203/ZEB2 and SNAI2	Suppresses colon cancer and liver metastasis.	[115]
RP11-757G1.5	↑	HT-29, SW620, SW480, HCT-116, LoVo, Caco-2, NCM460	Nude mice	CRC tissues = 56 samples	RP11-757G1.5, miRNA-139–5p, YAP1	Encourages CRC cell migration, invasion, and cell cycle progression.	[116]
miRNA-335–5p	↑	SW480, SW620	Mouse	Normal and CRC tissues	RASA1	Encourages the invasion, migration, and EMT of CRC cells.	[117]
miRNA-135b-5p	↑	HCT116, LoVo, MC38, HT29	Nude mice	CRC tissues = 94 pairs	TXNIP	Encourages CRC cell growth, migration, invasion, and angiogenesis while inhibiting apoptosis.	[118]
miRNA-3940–5p	↓	hUC-MSCs, DLD-1, HT-29, FHC	Athymic mice	–	ITGA6	Inhibits tumor metastasis and growth and prevents CRC cells' invasion and EMT.	[119]
miRNA-16–5p	↓	Caco-2, SW480, SW620, LoVo, HT29, NCM460	Nude mice	CRC tissues = 53 samples	ITGA2	Prevented CRC cells from proliferating, migrating, or invading while encouraging them to apoptosis.	[120]
miRNA-424	↓	NCM460, SW620, Lovo, SW480, CT-26, HCT-116	Nude mice	CRC = 65 samples	TGFBR3, Smad1	Inhibits CRC cells from migrating and invading, arrests the CRC cells in the G0/G1 phase, and encourages apoptosis in the CRC cells.	[121]
miRNA-934	↑	HCT-8, LoVo	–	Human CRC and adjacent normal mucosa samples	PTEN, PI3K/AKT signaling	Encourages CRC to metastasize to the liver.	[122]
miRNA-106b	↑	HCT116, HT29	Nude mice	CRC tissues = 91 samples	PDCD4, (PI3K)γ/ Akt/mTOR pathway	Induces M2 macrophage polarization and promotes EMT-mediated migration, invasion, and metastasis of CRC cells.	[123]
miRNA-27b-3p	↑	NCM460, LOVO, SW620, HCT-116, SW480, DLD-1	Nude mice	CRC tissue samples	hnRNPA1, STAT3	Increases blood artery permeability, encourages metastasis, and makes it easier for CTCs to form.	[124]
miRNA-106b-3p	↑	HCT116, SNU-C1, SW480, LoVo, SW1116, KM12SM, NCM460	Nude nice	CRC patients = 80 (including 40 mCRC patients and 40 non-mCRC patients) and 20 healthy people)	DLC-1	Increases CRC cell lung metastases by cell invasion, migration, and EMT.	[125]
miRNA-140–3p	↓	LoVo, HCT 116	Nude mice	- CRC blood = 70 case - Normal samples = 30 sample	BCL9 and BCL2	Suppresses migration, proliferation, invasion, and β-catenin nuclear translocation, inhibits liver metastasis, and promotes apoptosis.	[126]
miRNA-221/ 222	↑	SW480	Nude mice	Human CRC liver metastasis and adjacent noncancerous tissues	SPINT1, HGF	Increases the metastasis of the liver.	[127]
miRNA-203	↑	CaR-1, Colo205, RKO, Colo320DM, HCT116, DLD1, Lovo, SW480, HT29, SW620, THP-1	Nude mice	- CRC tissue = 88 pairs - Serum sample = 240 - BM samples = 10 sample	–	Encourages liver metastasis and the conversion of monocytes to M2-TAMs in CRC.	[128]

GEFH1 guanine nucleotide exchange factor for Rho family GTPases 1, *RhoA* ras homolog family member A, *TIMP3* tissue inhibitor of metalloproteinases 3, *ANXA2* annexin A2, *PD-L1* programmed cell death ligand 1, *TGF-β1* transforming growth factor beta 1, *TUBB3* tubulin beta 3, *INHBC* inhibin subunit beta C, *DGCR8* DiGeorge syndrome critical region gene 8, *DDX1* DEAD-box helicase 1, *ZEB2* zinc finger E-box binding homeobox 2, *SNAI2* snail family transcriptional repressor 2, *YAP1* yes-associated protein 1, *TXNIP* thioredoxin-interacting protein, *ITGA6* integrin subunit alpha 6, *ITGA2* integrin subunit alpha 2, *TGFBR3* transforming growth factor beta receptor 3, *PTEN* phosphatase and tensin homolog, *PI3K* phosphoinositide 3-kinase, *PDCD4* programmed cell death protein 4, *DLC-1* deleted in liver cancer 1, *BCL9* B-cell CLL/lymphoma 9, *BCL2* B-cell lymphoma 2, *SPINT1* serine peptidase inhibitor Kunitz type 1, *HGF* hepatocyte growth factor.

function [144]. Exosomal ncRNAs have been reported to promote the recruitment of immune-suppressive cells, such as myeloid-derived suppressor cells and regulatory T cells, to the tumor microenvironment [12]. These immune cells have the capacity to provide an immunosuppressive environment that fosters the growth and spread of tumors while reducing the anti-tumor immune response.

Exosomal ncRNAs can also affect how stromal cells and extracellular matrix elements behave [145]. They have the capacity to change the gene expression and activity of fibroblasts, which causes them to secrete substances that promote tumor cell invasion and progression [146]. Although they regulate the activity of endothelial cells and angiogenesis, which is essential for the development and dissemination of tumors [147]. The creation of innovative treatment modalities that target exosomal ncRNAs to prevent metastasis and enhance the effectiveness of cancer treatment may result from a better understanding of these mechanisms.

4.1.1. Exosomal ncRNA-mediated crosstalk between CAF and CRC cells in TME

CAFs are a significant part of the TME and are crucial for the growth and spread of tumors [148]. They influence the TME and the behavior of cancer cells through their interactions with immune cells, endothelial cells, and other stromal cells, like cancer cells [149]. Various ncRNAs, including miRNAs, circRNAs, and lncRNAs, can be found in exosomes released by both CAFs and CRC cells [150]. By transferring these exosomal ncRNAs, CAFs and CRC cells can communicate with one another and modify each other's biological processes [145].

CAFs secrete exosomes with versatile noncoding RNA payloads that phenotypically affect CRC recipient cells, leading to enhanced metastasis and chemoresistance [151]. For instance, by utilizing an orthotopic model, Bhome et al. found the significance of stromal miRNA-21 in the evolution of CRC progression and hypothesized that exosomes serve as a means of miRNA-21 delivery between cancer cells and stromal fibroblasts [152]. Similarly, Chen et al. confirmed that miRNA-93–5p from cancer-associated fibroblasts is transferred via exosomes, which causes FOXA1 to be downregulated and TGFB3 to be upregulated, increasing CRC cell radioresistance [153]. Likewise, by controlling the expression of *SNX2*, miRNA-181b-3p from CAFs enhances the onset and growth of CRC [154]. This has exposed a novel cancer-associated fibroblast (CAF) exosomal signature made up of miRNA-92a-3p [155], miRNA-17–5p [156], and miRNA-135b-5p [118], which have been demonstrated to affect a variety of cancer-relevant pathways in CRC tumors.

Additionally, CAF-exosomes transferred a high amount of lncRNA LINC00659 and enhanced CRC cells' proliferation, metastasis, and EMT via the miRNA-342–3p/ANXA2 pathway, where the exosomal lncRNA LINC00659 acted as a miRNA-342–3p sponge by lowering it and rising *ANXA2* expression [109].

Hypoxia, a significant regulator in the tumor microenvironment, can enhance exosome secretion from CAF in the CRC model. The hypoxia-induced exosomes were loaded with circEIF3K, which transferred to CRC cells and exerted oncogenic effects by enhancing CRC progression via modulating the circEIF3K/miRNA-214/PD-L1 axis [110]. Furthermore, CAFs also secrete exosomal circSLC7A6, which enhances CRC cell proliferation and invasion while inhibiting cell death. The CXCR5 chemokine receptor was identified as an effector of circSLC7A6-mediated tumorigenesis, while the above effects were inhibited by matrine treatment [157].

These interactions between CAFs and CRC cells mediated by exosomal ncRNAs contribute to the TME's formation, fostering a favorable environment for CRC development, invasion, and metastasis.

4.1.2. Exosomal ncRNA mediated cross talk between MSC and CRC cells in TME

Mesenchymal stem cells (MSC) are multipotent stem cells that are known to reside in bone marrow, fatty tissues, and dental pulp with the ability to migrate to inflammatory and tumor sites. They interact with tumor cells in primary and metastatic lesions and enhance EMT [158]. Exosomal ncRNA-mediated interaction between MSCs and CRC cells in TME is a dynamic mechanism that affects the growth and metastasis of the tumor [9]. MSCs, an essential element of the TME, can communicate with CRC cells by transferring exosomes that contain different ncRNAs [159]. These exosomal ncRNAs help MSCs and CRC cells communicate and modulate biological processes, altering the TME and tumor behavior.

Exosomes generated from MSCs and CRC cells include a variety of ncRNAs, including miRNAs, circRNAs, and lncRNAs. These exosomal ncRNAs can be transmitted from MSCs to CRC cells and have a variety of effects on processes connected to tumors. For example, Li et al. verified that by targeting *ITGA6* and then inactivating TGF-β1, MSC-exosomal miRNA-3940–5p prevents CRC cell invasion and EMT, as well as tumor development and spread [119]. Similarly, miRNA-16–5p was downregulated in CRC cells, and its target *ITGA2*, was highly expressed. Treating these CRC cells with bone marrow-derived MSC exosomes loaded with miRNA-16–5p successfully downregulated *ITGA2* and suppressed growth, migration, and invasion, accompanied by induced apoptosis of CRC cells in vitro, supported by reduced tumor growth in vivo [120]. Moreover, Zhang et al. revealed that suppressing miRNA-424 in BM-MSC exosomes suppressed malignant growth of CRC cells by upregulating *TGFBR3*, provided that they delineated upregulation of miRNA-424 and lowering of its target *TGFBR3* in CRC cells. As a result, both inhibition of miRNA-424 and upregulation of TGFBR3 resulted in upregulation of *p*-Smad1, inhibited metastasis of CRC cells, and increased CRC cell death. Furthermore, BM-MSCs' exosomal miRNA-424 encouraged the growth of CRCs [121]. Furthermore, exosomes can also be released by BM-MSCs to affect cancer cells. By downregulating Numb, a Notch signaling pathway inhibitor, Li and colleagues discovered that miRNA-142–3p derived from exosomes in BM-MSC caused colon cancer cells to exhibit characteristics of stem cells [160]. However, the TME exosomal ncRNAs mediate a complex and dynamic interaction between MSCs and CRC cells. Clarification of the precise ncRNAs implicated, their target genes, and the underlying mechanisms will require more study.

4.1.3. Exosomal ncRNA mediated cross talk between immunocytes and CRC cells in TME

In TME, exosomes are mediators of interaction between immune cells and tumor cells, thereby establishing premetastatic niches, immune surveillance, immune suppression, immune escape, and the tumor immune microenvironment [161–163]. Many immune cells infiltrate the TME, including macrophages, lymphocytes (B cells and T cells), neutrophils, NK cells, and dendritic cells [164]. One of the key immunological cells that promote tumor growth is the macrophage, which is identified in primary tumors and metastatic spread of CRC, where they are termed tumor-associated macrophages (TAM). These TAMs mediate tumor growth, angiogenesis, metastasis, and immunosuppression [165]. Immune cells communicate with CRC cells by transferring exosomes that contain different ncRNAs [166]. These exosomal ncRNAs support reciprocal interactions and cellular function modification between

immunocytes and CRC cells, which influences tumor development within the TME and the anti-tumor immune response [14].

Exosomes produced by immunocytes and CRC cells both contain several ncRNAs, including miRNAs, lncRNAs, and other RNA species. For instance, in human progenitor cells, miRNA-20a, miRNA-17–5p, and miRNA-106a overexpression suppressed *AML1* by attaching to the promoter and reducing *M-CSFR*, which caused the MDSC to differentiate [167]. Similarly, in order to encourage the development of MO-MDSCs by IL6-induced m6A alteration, the highly expressed lncRNA pseudogene *olfr29-ps1* downregulated miRNA-214–3p [168]. Likewise, according to Liang et al., the exosomal lncRNA RPPH1 produced by CRC cells caused macrophages to polarize into the M2 form, which in turn encouraged the metastasis and development of CRC cells [169]. Moreover, circPACRGL, identified by Shang et al. as a new CRC-driven exosomal circRNA, enhanced CRC proliferation and metastasis by targeting the miRNA-142–3p/miRNA-506-3p-TGF-β1 axis, and with this pathway, it induced N1 to N2 neutrophil differentiation [111]. Although miRNA-934 was packaged into CRC cells' exosomes by hnRNPA2B1, which then delivered exosomal miRNA-934 to macrophages, Zhao et al. demonstrated that exosomal miRNA-934 from CRC cells boosted PI3K/AKT signaling and suppressed PTEN expression to polarize M2 macrophages [122]. Exosomal transfer of miRNA-106b [123] and miRNA-21–5p [170] is another fundamental mechanism by which EMT of CRC induces M2 polarization of TAM.

In addition, exosomal lncRNAs also played significant roles in the immunological escape process in the CRC microenvironment, where exosomal lncRNA SNHG10, driven by EMT-CRC cells, inhibited NK cell activity by upregulating inhibin subunit beta C (INHBC) and activating the TGF-β axis in NK cells [113]. Furthermore, CRC derived exosomes transported the lncRNA RPPH1 into macrophages, where it promoted polarization of macrophage M2 and consequently metastasis of CRC cells [112].

4.1.4. Exosomal ncRNA mediated effect on EMT, migration and invasion in TME

EMT is a process that is essential for cancer cells to acquire the ability to spread metastatically, and it is marked by a loss of epithelial characteristics and a rise in mesenchymal characteristics. EMT is also correlated with cancer induction, migration, therapy resistance, and a poor prognosis [171,172]. Exosomes released from EMT-CRC cells were reported to be loaded with miRNA-27–3p, promote metastasis by increasing vascular permeability, and support the generation of circulating tumor cells (CTC). Hence, clinically, CRC patients' plasma exosomal miRNA-27b-3p level showed a positive correlation with disease progression and CTC counts [124].

Exosomal ncRNA is essential for regulating several biological processes in the TME, like migration, invasion, and the EMT [173]. Among them, exosomal miRNAs play a critical role in the regulation of migration, invasion, and EMT. For instance, Guo et al. demonstrated that exosomes from Fusobacterium nucleatum-infected cells were used to transfer miRNA-1246, 92b-3p, 27a-3p, and CXCL16/RhoA/IL-8 into uninfected cells, increasing cell migratory capacity in vitro and promoting metastasis of tumors in vivo [174]. Similarly, exosome-enriched miRNA-210 secreted from primary CRC cells communicates with neighboring disseminated metastatic cells to promote EMT signaling and guide metastatic cells to disseminate to new free-metastatic sites [175]. Likewise, Liu and colleagues demonstrate that miRNA-106b-3p can be transported by exosomes from CRC cells with a high propensity for invasion to CRC cells with a low propensity for invasion, boosting CRC cell metastasis through *DLC-1* targeting as well as increasing CRC cell lung metastasis in vivo [125].

In contrast, some exosomal cargo miRNAs may also be downregulated. For example, Liu and his collaborators showed that miRNA-140–3p was reduced in both serum exosomes of patients with CRC or CRC with LM and tissues of CRC patients in comparison with normal controls and healthy patient tissue samples, respectively. Further confirmation that by targeting *BCL9* and *BCL2*, miRNA-140–3p acts as a tumor suppressor in the advancement of CRC is needed, and this suggests that the miRNA-140-3p-BCL9/BCL2 axis may be applied to CRC prognostication and miRNA-based treatment [126]. Similarly, miRNA-375–3p was shown to be inversely associated with EMT in cancer. Rezaei et al. found in their assay that delivery of exosomal miRNA-375–3p mimic isolated from HT-29 and SW480 CRC cell lines minimized the process of EMT and the migration and invasion abilities of CRC cell lines, indicating that these tumor-derived exosomes may be an effective treatment option for mCRC [176].

CircRNA also participates in enhancing the invasion and migration capacities of CRC cells. For example, circLONP2 on an intracellular level promotes maturation of primary miRNA-17 in a dead box protein family (DDX1)-dependent manner by recruiting Drosha complex and DiGeorge syndrome critical region gene 8 (DGCR8), while intercellularly it promotes the transfers of mature miRNA-17–5p via exosomes to neighboring cells, enhancing their aggressiveness and resulting in metastasis initiation in the primary tumor locus as well as acceleration in the metastatic spread to distant organs [114]. Thus, exosomal ncRNAs have complicated interactions with their target molecules in the TME, and a better understanding of these interactions can lead to the creation of novel treatment approaches that suppress cancer metastasis and enhance patient outcomes.

4.2. Exosomal ncRNA remodel the PMN to mediate metastasis process

The concept of PMN was first proposed by Kaplan and his colleagues in 2005 with the finding of a relationship between the hematopoietic progenitor complex with VEGFR1+ and VLA-4+ and the spread of organ-specific tumors [177]. PMN is the circulating tumor cells' (CTC) destination in distant organs or a predetermined location where they colonize and metastasize. Exosomes are major regulators and players in the PMN microenvironment, in which they facilitate perfecting the prerequisite characteristics of a PMN, including inflammation, lymphangiogenesis, angiogenesis, immunosuppression, and organotropism [178–180].

4.2.1. Exosomal ncRNA and stromal cell activation in PMN

Exosomal membrane protein ADAM17 aids in the formation of PMN by cleaving the *E*-cadherin junction and enhancing EMT of CRC cells, specifically inducing liver metastasis (LM) in vivo [62]. Hepatic stellate cells (HSC) activation remodels liver TME by releasing growth factors (metalloproteinases, insulin-like growth factor, VEGF, and TGF-β) [181]. In an assay, HSC were incubated with CRC cell-derived exosomes, and HSP111 was revealed as a major upregulated gene in this study. Furthermore, an in vivo xenografted mouse model illustrated that these CRC cells drive exosomal HSP111-mediated PMN formation and CRC-associated liver metastasis [182]. The underlying mechanism for the liver metastasis was associated with CAFs, in which HSP111 affected the lipid metabolism of CAFs by increasing the level of acetyl-Co-A, which increased H3K27 acetylation in CAFs, resulting in overexpression of CLCX5. Exosomal HSPC111 secretion from CRC cells was stimulated via the CXCL5-CXCR2 axis and further promoted PMN formation and liver metastasis [182].

Another set of genes, miRNA-221/222, are involved with mCRC through their in vitro and in vivo experiments. Tian and his collaborators demonstrated that exosomes enriched with this miRNA cluster suppressed *SNIP1* expression, activated hepatocyte growth factor in the liver, and supported the formation of favorable PMN to initiate liver metastasis and aggressive CRC phenotyping. Additionally, serum exosome levels were found to be elevated in patients with CRC liver metastasis [127].

4.2.2. Exosomal ncRNA enhance angiogenesis and vascular permeability in the PMN

The development of new blood vessels, or angiogenesis, is an

essential mechanism for promoting the expansion and survival of metastatic cells within PMNs [183]. By modulating several cellular elements involved in this process, exosomal ncRNAs have been demonstrated to encourage angiogenesis [147]. For instance, exosomal miRNA-25–3p from CRC was found to mediate liver and lung metastasis by increasing vascular leakiness and angiogenesis [133]. MiRNA-25–3p is transmitted from the CRC to endothelial cells by means of exosomes, where it will promote angiogenesis and vascular permeability by regulating the expression of *VEGFR2*, *ZO-1*, *occludin*, and *Claudin5* inside endothelial cells, consequently impairing the junction between endothelial cells via targeting the Krüppel-like factor family (KLF2 and KLF4) [133]. While conflictingly, exosomal angiopoietin-like protein 1 (ANGPTL1) was found to attenuate LM of CRC by means of reducing vascular leakiness and reprogramming Kupffer cells in liver PMN. Mechanistically, Kupffer cells take up exosomal-ANGPTL1 and inhibit the JAK2-STAT3 signaling axis, resulting in downregulation of MMP9 and impeding vascular leakiness [184].

4.2.3. Exosomes and lymphangiogenesis in PMN

Lymphangiogenesis is the process by which new lymphatic vessels are created [185]. These new lymphatic channels are vital for immune monitoring, fluid equilibrium, and the transportation of immune cells and antigens [186]. For instance, Sun and his colleagues showed in their in vivo and in vitro experiments that macrophage uptake of CRC-derived exosomes enhances VEGF-C secretion, increases lymphatic endothelial cell proliferation, and mediates sentinel lymph node (SLN) metastasis of CRC. These findings suggest that exosomes secreted from CRC can stimulate lymphangiogenesis and remodel the PMN to mediate sentinel lymph node (SLN) [187]. The frequency of F4/80+ macrophages in SLN was increased by these exosomes. VEGFC release and the frequency of F4/80+ macrophages were shown to be increased by exosomal interferon regulatory factor 2 (IRF2). Exosomal IRF-2 may be used to predict CRC-LN metastasis because it was also discovered that CRC patients with LN (lymph node) metastases had serum exosomal levels of IRF2 that were substantially higher than healthy control group values [187].

4.2.4. Inflammation and ncRNA exosomes in PMN

A crucial part of generating a favorable environment for metastatic cells is inflammation, which is characterized by immune cell infiltration, cytokine release, and tissue remodeling [188]. Exosomes generated by tumor cells have the ability to transmit certain miRNAs to PMN immune cells like macrophages. Macrophages have a flexible functional architecture; traditionally activated macrophages release type I (M1) cytokines that are pro-inflammatory and have anti-tumorigenic properties [189]. For instance, Wang et al. revealed that multiple miRNAs, including miRNA-25–3p, miRNA-130b-3p, and miRNA-425–5p, are delivered to macrophages by CXCR4-overexpressing CRC cells via exosomes. This causes macrophages to become M2 polarized via the PTEN/PI3K/Akt pathway, which in turn increases the ability of CRC to metastasize by encouraging EMT and secreting vascular endothelial growth factor (VEGF) [190]. Similarly, Shao and colleagues confirmed that CRC can synthesize exosomes that are targeted toward liver tissues to induce polarization of macrophages toward IL-6-secreting proinflammatory phenotyping with the aid of cargo miRNA-21–5p, which is highly enriched in these exosomes. MiRNA-21 targets toll-like receptor 7 (TLR7) in macrophages to ignite an inflammatory PMN. In addition, serum exosomes from mCRC patients in the liver were also found to be enriched with miRNA-21 [191].

4.2.5. Immunosuppression and ncRNA exosomes in PMN

One of the distinguishing features of PMN formation in mCRC is the recruitment of immune cells to create an immunosuppressive milieu [192]. For example, CRC-derived exosomes enriched with miRNA-203 are incorporated into monocytes where they promote differentiation of these monocytes, into M2-TAMs and mediate LM in CRC [128]. Hypoxia and immunosuppression were two hallmarks elucidated by Sun et al. in their study to mediate CRC metastasis via exosomes. Through their in vivo and in vitro experiments, they confirmed that a hypoxic primary TME promotes exosome release from primary CRC lesions to establish and initiate a prerequisite PMN specifically and selectively in liver only, where Kupffer cells engulfed exosomes enriched with miRNA-135a-5p from circulation into liver [193]. Exosomal miRNA-135a-5p started PMN formation in the liver, supporting CRC cell adhesion through the miRNA-135a-5p-LATS2/YAP1-MMP7 pathway axis with the help of exosomal miRNA-135a-5p-mediated CD30-TRAF2-NF-κB-immunosuppression signaling. Moreover, the authors noted that both in tumoral and serum samples of CRC patients, there were elevated levels of miRNA-135a-5p, which was correlated with poor prognosis and liver metastasis. Likewise, polarized M2 macrophages secreting exosomal miRNA-934 mediate the formation of PMN and promote liver metastasis of CRC by secreting CXCL13. In CRC cells, CXCL13 activates a CXCR5, CXCL13, p65, NF-κB, and miRNA-934 positive feedback loop [122].

4.2.6. Organotropism and exosomes in PMN

Organotropism is cancer metastasis to specific organs, also called "organ-specific metastasis." Several types of cancer feature distinct organotropism; for instance, CRC metastasizes preferably to the liver [194,195]. Tumor-derived exosomes display specific integrins on their membrane that interact with the extracellular matrix and prepare the formation of PMN in destined organs [196].

Proteomic analysis of exosomes driven from lung and liver metastasis cells showed distinct integrin expression patterns. Integrins α6β4 and α6β1 are enriched in exosomes with lung tropism, while exosomal integrins αvβ5 are enriched in exosomes with liver tropism. These exosomes fuse with fibroblasts and epithelial cells in the lung and with Kupffer cells in the liver. Exosome uptake by these cells induces two cellular processes, namely, Src phosphorylation and pro-inflammatory S100 gene expression, promoting organ-specific metastasis [180,197]. In another assay, the integrin α5β1 expressed on the surface of CRC cells and peritoneal mesenchymal cells dictated the peritoneal metastasis of CRC cells by interacting with their ligand, Dis-ADAM 17, expressed on exosomes derived from CRC cells, consequently enhancing exosomal uptake by CRC and peritoneal mesenchymal cells. While the presence of tetraspanin CD9 on the exosomal surface acted as a negative regulator of this process [198].

5. Therapeutic strategies of exosome-based tumor suppression

Exosomes are a major component of cellular communication, and they transfer a wide array of bioactive compounds, representing an effective vehicle for the delivery of versatile substances like drugs, lipids, proteins, and nucleic acids (like ncRNA and siRNA) [199]. Exosomes, from a therapeutic viewpoint, can be used as vehicles for other therapeutics, and genetic substances or exosomes can be therapeutic targets for other drugs (Table 2). Hence, they gained paramount attention in recent years as effective anticancer vehicles because of their good biocompatibility and inherent low immunogenicity properties [200].

Exosomes can be driven from different sources and cell types, e.g., milk-derived exosomes, MSC-derived exosomes, dendritic cell-derived exosomes, HEK293 cell-derived exosomes, erythrocyte-derived exosomes, and cancer cell-derived exosomes, with each type having its own specific pros and cons [201].

Furthermore, targeting exosomes or exosomal pathways using other medications or herbal treatments to inhibit exosome secretion, production, or their cell-to-cell interconnection has the potential to disarrange cancer cell communication [202].

5.1. Exosomes as vehicle for cancer therapeutic

The potential use of the exosome as a carrier to deliver various anticancer treatments or molecules to cancer cells comes in many forms. For

Table 2
Effects of several types of drugs on exosomal ncRNA signaling pathway regulation.

Type of Drugs	Non-coding RNA	Expression	Effect	Axis	Ref.
5-fluorouracil and Oxaliplatin	CRNDE	↑	Decreased sensitivity	miRNA-181a-5p/Wnt/β-catenin pathway	[220]
Oxaliplatin	MIR600HG	↓	Promote sensitivity	ALDH1A3	[221]
Oxaliplatin	MALAT1	↑	Promote resistance	MALAT1/miRNA-218/EZH2	[222]
5-fluorouracil	CCAT1	↑	Promote sensitivity	–	[223]
Cisplatin	LINC00261	↓	Promote sensitivity	Wnt/β-catenin pathway	[224]
Oxaliplatin	Linc00152	↑	Promote resistance	miRNA-193a-3p/AKT/ERBB4 axis	[225]
Oxaliplatin	HOTAIR	↑	Promote resistance	HOTAIR/miRNA-1277–5p/ZEB1	[226]
5-fluorouracil		↑	Promote resistance	miRNA-218/NF-κB/TS	[227]
Oxaliplatin	OIP5-AS1	↑	Promote resistance	OIP5-AS1/miRNA-137	[228]
Adriamycin	BANCR	↑	Promote resistance	miRNA-203/CSE1L	[229]
5-fluorouracil and Oxaliplatin	GIHCG	↑	Promote resistance	–	[230]
Oxaliplatin	CACS15	↑	Promote resistance	miRNA-145/ABCC1	[231]
Oxaliplatin	CBR3-AS1	↑	Promote resistance	miRNA-145–5p	[232]
Oxaliplatin	CRNDE	↑	Promote resistance	miRNA-136/E2F1	[233]
Oxaliplatin	KCNQ1OT1	↑	Promote resistance	miRNA-34a/ATG4B	[234]
Oxaliplatin	MIR155HG	↑	Promote resistance	miRNA-650/ANXA2	[235]
Oxaliplatin	lnc-RP11-536 K7.3	↑	Promote resistance	SOX2/HIF-1α/USP7	[236]
Oxaliplatin	TUG1	↑	Promote resistance	GATA6-BMP	[237]
Oxaliplatin	PiHL	↑	Promote resistance	EZH2/HMGA2/PI3K/Akt	[238]
Oxaliplatin	ELFN1-AS1	↑	Promote resistance	EZH2/DNMT3a/MEIS1	[239]
Oxaliplatin	NBAT-1	↓	Promote sensitivity	miRNA-4504/WWC3/LATS1/YAP	[240]
FOLFOX Regimen	PVT1	↓	Promote sensitivity	hsa-miRNA-297/GSTA2	[241]
5-fluorouracil, doxorubicin, and cisplatin	miRNA-138–5p	↓	Promote sensitivity	NFIB-Snail1 axis	[242]
Oxaliplatin	miRNA-744	↑	Promote resistance	BIN1	[243]
Oxaliplatin	miRNA-5000–3p	↑	Promote resistance	USP49	[244]
Oxaliplatin	miRNA-19b-3p	↑	Promote resistance	SMAD4	[245]
Oxaliplatin	miRNA-454–3p	↑	Promote resistance	PTEN	[246]
Oxaliplatin	miRNA-503–5p	↑	Promote resistance	PUMA	[247]
Oxaliplatin	miRNA-107	↑	Promote resistance	CAB39/AMPK/mTOR	[248]
Oxaliplatin	miRNA-135b-5p	↑	Promote resistance	MUL1/ULK1	[249]
Oxaliplatin	miRNA −506	↓	Promote sensitivity	MDR1/P-gp/Wnt/β-catenin	[250]
Oxaliplatin	miRNA-200b-3p	↓	Promote sensitivity	TUBB3	[251]
Oxaliplatin	miRNA-122	↓	Promote sensitivity	XIAP	[252]
Oxaliplatin and 5-fluorouracil	miRNA-193a-5p	↓	Promote sensitivity	CXCR4	[253]
Oxaliplatin	miRNA-483–3p	↓	Promote sensitivity	FAM171B	[254]
Oxaliplatin	miRNA-325	↓	Promote sensitivity	HSPA12B/PI3K/AKT/Bcl-2	[255]
Oxaliplatin	miRNA-34a	↓	Promote resistance	TGF-β/Smad4 pathway	[256]
5-fluorouracil	miRNA-129	↓	Promote sensitivity	BCL2	[257]
Doxorubicin	miRNA-195	↓	Promote sensitivity	BCL2L2	[258]
5-fluorouracil	miRNA-135b and miRNA-182	↑	Promote resistance	ST6GALNAC2/PI3K/AKT	[259]
5-fluorouracil	miRNA-26b	↓	Promote sensitivity	Pgp	[260]
5-fluorouracil	miRNA-22	↓	Promote sensitivity	BTG1	[261]
5-fluorouracil	miRNA-361	↓	Promote sensitivity	FOXM1-ABCC5/10	[262]
5-fluorouracil	miRNA-577	↓	Promote sensitivity	HSP27	[263]
Doxorubicin	miRNA-223	↑	Promote resistance	FBXW7	[264]
Oxaliplatin and 5-fluorouracil	CircPTK2	↑	Promote resistance	miRNA-136–5p/YTHDF1	[265]
Oxaliplatin and 5-fluorouracil	Circ_0032833	↑	Promote resistance	miRNA-125–5p/MSI1	[266]
Oxaliplatin	Hsa_circ_0079662	↑	Promote resistance	miRNA-324–5p/TNF-α/HOXA9	[267]
Oxaliplatin	CircHIPK3	↑	Promote resistance	miRNA-637/STAT3/Bcl-2/beclin1	[268]
Irinotecan	Circ_001680	↑	Promote resistance	miRNA-340/BMI1	[269]
Oxaliplatin	CiRS-122	↑	Promote resistance	miRNA-122/PKM2	[270]
5-fluorouracil	Circ-PRKDC	↑	Promote resistance	miRNA-375/FOXM1 axis and Wnt/β-Catenin pathway	[271]

instance, exosomes can be used to deliver targeted chemotherapy to increase efficacy, decrease adverse effects on normal cells, and overcome resistance mechanisms [203]. For example, MUC1 aptamer-decorated MSC-derived exosomes used to deliver doxorubicin to colon adenocarcinoma exhibited favorable biodistribution, represented by elevated accumulation in tumor tissue and quicker liver clearance. It also significantly suppressed tumor growth compared with the free form of doxorubicin [204]. Similarly, Xu et al. illustrated that DC-derived exosomes uploaded with the chemotherapeutic drug 5-FU showed favorable anticancer effects against CRC cells in vivo, in which part of this effect was attributed to DC-derived exosomes. As a carrier, they showed a trend of tumor growth suppression and enhanced anti-tumor effects of 5-FU [205]. It has been well documented that chemotherapy-induced adverse drug reactions, among others, negatively impact the quality of life of adult cancer patients [206]. Therefore, if exosomes as carriers can minimize chemotherapy-induced adverse drug effects, they could be translated into real-life use to elevate patients' quality of life.

Moreover, exosomes can be used to deliver specific ncRNA to interfere with an important pathway or a cancer hallmark, as shown in the study by Yao and his collaborators, where they successfully delivered miRNA-204–5p via exosomes driven from HEK293 cells to several cancer cell types, with both in vivo and in vitro results showing that these exosomes prevented proliferation, induced apoptosis, and increased 5-FU chemosensitivity of CRC cells and other types of tumor cells by decreasing *RAB22A* and *Bcl-2* gene expression [207].

Furthermore, exosomes are used for co-delivery of ncRNA-chemotherapy; this methodology was applied by Liang and his collaborators, where they used engineered exosomes for simultaneous delivery of 5-FU and miRNA-21 suppressor oligonucleotides to both the 5-FU-

resistant CRC HCT-1165FR cell line and a tumor-bearing mouse model. The results were promising, in which this combinatorial delivery effectively reversed 5-FU therapeutic resistance and induced its cytotoxicity in resistant CRC cells [208]. In another study, engineered exosomes were used for the purpose of co-delivery of the lncRNA PGM5-AS1 and oxaliplatin, where oxaliplatin resistance is an obstacle faced by almost all patients with mCRC. This combination successfully reversed oxaliplatin resistance both in vivo and in vitro and attenuated the malignant phenotype of CRC mechanistically by both alternative splicing activation via recruiting SRSF3 to reduce expression of *PAEP* and upregulating *NME1* through sponging hsa-miRNA-423–5p [209].

In addition, exosomes can be utilized to deliver repurposed drugs that have anticancer properties to the TME. The nano-amorphous aspirin-loaded exosomes exemplified the applicability of this approach, where in vitro experiments showed increased cellular uptake and cytotoxicity of aspirin to CRC cells and eradicated cancer stem cells. It also enhanced apoptosis and autophagy. In vivo experiments showed improved delivery of aspirin to the CRC tumor by adding an aptamer to specifically target the EpCAM protein [210]. Similarly, exosomes from hepatocellular carcinoma treated with melatonin can change the immune suppression status by reducing STAT3 activation, resulting in reduced expression of *PD-L1* on macrophages and the release of inflammatory cytokines [211]. A registered, ongoing phase 1 clinical trial (NCT01294072) examines the efficacy of plant-based exosomes as carriers for the anti-tumor drug curcumin taken by oral route in colon cancer patients by comparing a group who takes curcumin only with another group taking curcumin conjugated with plant exosomes [212].

5.2. *Exosomes as therapeutic target*

Exosomes themselves can be targeted for medical treatment. Interfering with exosome synthesis, release, or function can have therapeutic advantages since exosomes participate in cell-to-cell communication and can aid in cancer development and metastasis [213]. Exosome synthesis can be decreased by inhibiting the biogenesis and secretion processes. For instance, by reducing PPARα enrichment on the lncRNA-APC1 promoter, APC may increase the expression of lncRNA-APC1, which was adequate to stop CRC cell proliferation, spread, and tumor angiogenesis by preventing the generation of exosomes via the direct binding of Rab5b mRNA and a decrease in its stability [214]. Similarly, ISG15 expression and conjugation to MVB proteins like TSG101 are induced by IFN-I. ISGylation of MVB proteins encourages MVB fusion with lysosomes and destruction, preventing the release of exosomes [215] (Fig. 4). Besides that, Zhao et al. approve that apatinib reduced the expression of SNAP23 and VAMP2, which prevented MVB membrane fusion, suppressed orthotopic mouse colon cancer development and metastasis in vivo, and decreased the quantity of serum exosomes [216].

Moreover, exosomes are ingested by recipient cells by numerous processes, including membrane fusion, phagocytosis, and endocytosis [217]. The delivery of pro-tumorigenic signals delivered by exosomes can be decreased by blocking these absorption routes. Inhibiting some receptor-ligand interactions necessary for exosome absorption, such as those involving integrins or tetraspanins, can prevent recipient cells from absorbing exosomes. For instance, dendritic cell absorption of EVs

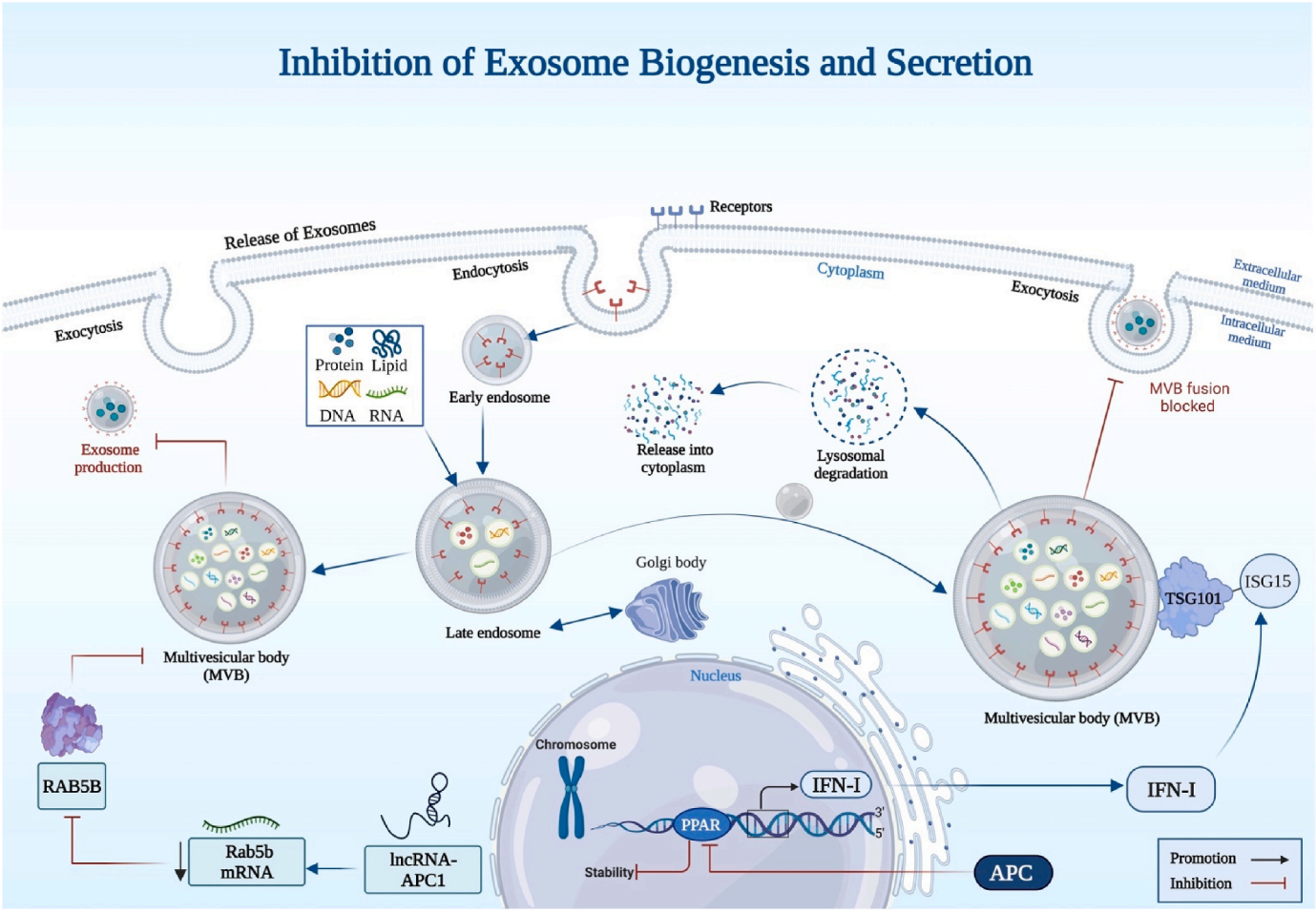

Fig. 4. Illustration shows that by preventing biogenesis and secretion, exosome synthesis can be reduced. By directly lowering Rab5b mRNA stability and exosome formation in CRC cells, lncRNA-APC1, a crucial APC mediator, prevents the spread of CRC. ISG15 is expressed and coupled to MVB proteins, such as TSG101, by IFN-I. Inhibiting exosome secretion, ISGylation of MVB proteins encourages MVB fusion with lysosomes and destruction.

is decreased when recipient cells are treated with antibodies against the tetraspanins CD81 or CD9 [218]. Similarly, dendritic cell absorption of EVs can be decreased by antibodies that block the binding sites of CD11a or its ligand, ICAM-1. Similar outcomes were seen after inhibiting integrins v (CD51) and 3 (CD61) on the surface of dendritic cells [218].

Another approach in exosomal therapeutic strategy may be inhibiting certain exosomal pathways involved with metastasis of CRC. Dahuang zhechong pill (DZP) is a well-known formula from "Synopsis of Prescriptions of the Golden Chamber" used for thousands of years in the treatment of abdominal masses and recently proved to suppress CRC liver metastasis via both marked suppression of upregulated exosomal CC chemokine ligand-2 (CCL2) and its receptor CCR2 in the liver and attenuated exosomal-CCL2-induced M2 polarization [219]. Additionally, matrine, traditionally used in CRC treatment, was reported to reduce CRC tumorigenicity by inhibiting exosomal circSLC7A6 secretion from CAFs [157].

However, it is important to note that exosome-based medicines are still in their infancy, and additional study is required to improve their targeting approaches, assess their safety histories, and ascertain their efficacy in clinical settings.

ALDH1A3 aldehyde dehydrogenase 1 family member A3, *MALAT1* metastasis associated lung adenocarcinoma transcript 1, *EZH2* enhancer of zeste homolog 2, *ERBB4* erb-B2 receptor tyrosine kinase 4, *AKT* v-akt murine thymoma viral oncogene homolog, *HOTAIR* HOX transcript antisense RNA, *ZEB1* zinc finger E-box-binding homeobox 1, *OIP5-AS1* opa interacting protein 5-antisense RNA 1, *CSE1L* chromosome segregation 1 like, *ABCC1* ATP binding cassette subfamily C member 1, *E2F1* E2F transcription factor 1, *ATG4B* autophagy related 4B cysteine peptidase, *ANXA2* annexin A2, *SOX2* SRY-box transcription factor 2, *HIF-1α* hypoxia inducible factor 1 subunit alpha, *USP7* ubiquitin specific peptidase 7, *GATA6* GATA-binding protein 6, *BMP* bone morphogenetic protein, *HMGA2* high mobility group AT-hook 2, *PI3K* phosphatidylinositol 3-kinase, *DNMT3a* DNA methyltransferase 3 alpha, *MEIS1* meis homeobox 1, *LATS1* large tumor suppressor kinase 1, *YAP* yes-associated protein 1, *GSTA2* glutathione S-transferase alpha 2, *NFIB* nuclear factor 1 B-type, *BIN1* bridging integrator 1, *USP49* ubiquitin specific peptidase 49, *SMAD4* mothers against decapentaplegic homolog 4, *PTEN* phosphatase and tensin homolog, *PUMA* p53 upregulated modulator of apoptosis, *CAB39* calcium-binding protein 39, *AMPK* AMP-activated protein kinase, *mTOR* mammalian target of rapamycin, *MUL1* mitochondrial e3 ubiquitin protein ligase 1, *ULK1* unc-51-like autophagy activating kinase 1, *MDR1* multidrug resistance protein 1, *TUBB3* tubulin beta 3 class III, *XIAP* X-linked inhibitor of apoptosis protein, *CXCR4* C-X-C chemokine receptor type 4, *FAM171B* family with sequence similarity 171 member B, *HSPA12B* heat shock protein family A (Hsp70) member 12B, *Bcl-2* B-cell lymphoma 2, *TGF-β* transforming growth factor beta 1, *BCL2* B-cell lymphoma 2, *BCL2L2* Bcl-2-like protein 2, *ST6GALNAC2* ST6 *N*-acetylgalactosaminide alpha-2,6-sialyltransferase 2, *BTG1* BTG anti-proliferation factor 1, *FOXM1* forkhead box protein M1, *ABCC5/10* ATP-binding cassette subfamily C member 5/10, *HSP27* heat shock protein 27, *FBXW7* f-box and wd repeat domain containing 7, *TNF-α* tumor necrosis factor-alpha gene, *HOXA9* homeobox A9, *STAT3* signal transducer and activator of transcription 3, *PKM2* pyruvate kinase muscle 2.

6. Conclusions and perspectives

Cancer hallmark research has been very well identified in previous years and has led scientific research toward focusing on the primary TME and the metastatic tumor microenvironment ("PMN"). Eventually, much recent research focused on identifying morphological and structural modifications in the TME and, to a lesser extent, on the PMN. Focusing on fine-tuning factors and carriers that modulate these structural and morphological changes within TME and then into the PMN will help in further elucidating the micro-mechanisms underlying CRC metastasis and in better advancement of therapeutic management strategies. Cancer cells secrete exosomes into the TME, and these exosomes frequently ferry metastasis signals far up to metastatic spread locations or the PMN. Among exosomal cargos, exosomal ncRNAs have been shown to play a substantial role in reshaping the TME and PMN of CRC. Exosomal ncRNA regulates signaling pathways between CRC cells and other cells in the TME, like fibroblasts, mesenchymal cells, neutrophils, and macrophages, among others. Furthermore, the aberrant expression of exosomes and exosomal ncRNA in the PMN directly or indirectly promotes metastasis processes from inflammation, lymphangiogenesis, angiogenesis, immunosuppression, and organotropism. Further research on metastasis mechanisms in the PMN will provide a broad prospect for either preventing or treating CRC metastasis. Additionally, exosomal ncRNAs have been identified in the study as possible therapeutic targets for CRC metastasis. These exosomal ncRNAs' packaging, secretion, or absorption may be affected by therapeutic interventions, opening up new possibilities for preventing metastasis and enhancing patient outcomes.

The existing gap between the research progress on exosomal ncRNA and their role in the TME, PMN, and clinical practice cannot be ignored. More research and clinical trial studies are required in this field. Specifically, we believe our review and similar reviews will help in identifying signature ncRNAs involved in CRC development and metastasis to be targeted collectively. This may result in an unexpected level of therapeutic management for CRC.

Abbreviations

ABCC1	ATP binding cassette subfamily C member 1
ALDH1A3	Aldehyde dehydrogenase 1 family member A3
Alix	Apoptosis linked gene 2-interacting protein
AMPK	AMP-activated protein kinase
ANXA2	Annexin A2
BCL2	B-cell lymphoma 2
BIN1	Bridging integrator 1
BM-MSCs	Mesenchymal stem cells produced from bone marrow
BMP	Bone morphogenetic protein
CAB39	Calcium-binding protein 39
CHMP2B	Charged multivesicular body protein 2B
DLC-1	Deleted in liver cancer 1
EZH2	Enhancer of zeste homolog 2
FBXW7	F-box and wd repeat domain containing 7
GEFH1	Guanine nucleotide exchange factor for Rho family GTPases 1
GSTA2	Glutathione S-transferase alpha 2
HGF	Hepatocyte growth factor
HIF-1α	Hypoxia inducible factor 1 subunit alpha
HOXA9	Homeobox A9
INHBC	Inhibin subunit beta C
ITGA6	Integrin subunit alpha 6
m6A	N6-methyladenosine
MALAT1	Metastasis associated lung adenocarcinoma transcript 1
MDR1	Multidrug resistance protein 1
MUL1	Mitochondrial e3 ubiquitin protein ligase 1
NFIB	Nuclear factor 1 B-type
PD-L1	Programmed cell death ligand 1
PKM2	Pyruvate kinase muscle 2
PTEN	Phosphatase and tensin homolog
PUMA	p53 upregulated modulator of apoptosis
RhoA	Ras homolog family member A
SMAD4	Mothers against decapentaplegic homolog 4
SNAI2	Snail family transcriptional repressor 2
SOX2	SRY-box transcription factor 2
STAT3	Signal transducer and activator of transcription 3
TGF-β1	Transforming growth factor beta 1
TIMP3	Tissue inhibitor of metalloproteinases 3
TNF-α	Tumor necrosis factor-alpha gene
TSG 101	Tumor susceptibility gene 101 protein

TUBB3	Tubulin beta 3 class III
USP7	Ubiquitin specific peptidase 7
VPS	Vacuolar protein sorting proteins
YAP	Yes-associated protein 1
ZEB2	Zinc finger E-box binding homeobox 2

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