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The Role of Macrophage-Derived Extracellular Vesicles in Gastrointestinal Cancers

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Abstract: Extracellular vesicles are lipid-bound vesicles derived from cells that can interact with other cells, participate in cell signaling, and transfer biologically active molecules. The pro-tumorigenic role of extracellular vesicles has been extensively investigated. The production of these vesicles occurs in both physiological and pathological processes by many cell types, including the macrophages. Macrophages have differential role in tumor biology: the M1 macrophages are cytotoxic (anti-tumor activity), and the M2 macrophages are pro-tumorigenic. A subpopulation of these macrophages is described as tumor-associated macrophages and several studies have described the importance of extracellular vesicles

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derived from tumor-associated macrophages in the advancement and progression of gastrointestinal cancers. This chapter highlights the role of macrophage-derived extracellular vesicles in gastric, hepatic, pancreatic, and colorectal tumors. It also discusses the importance of molecules and cell signaling pathways involved in this context and emphasize the relevant role of these extracellular vesicles in tumor development.

Keywords: extracellular vesicles in gastrointestinal cancers; gastrointestinal cancer; macrophage; macrophage-derived extracellular vesicles; microRNA.

INTRODUCTION

Extracellular vesicles (EVs) are lipid-bound small vesicles derived from the plasma membranes or interior of the cells. EVs are divided into two main groups: larger EVs or microparticles (100 nm to 1000 nm in diameter), and smaller EVs or exosomes (10 to 150 nm in diameter). Apart from these, apoptotic bodies, formed during the final stages of cellular apoptosis, are also considered a type of EV (1, 2). EVs are crucial for cell signaling and transferring biologically active molecules such as lipids, proteins, and nucleic acids. EVs can interact with other cells through the delivery of compartmentalized material or can be taken up by target cells. The production of EVs occur both in physiological and pathological conditions such as cancer (3). Studies associate the presence of EVs with tumor development, invasion, angiogenesis, and metastasis (3). Studies on the interaction of tumor-derived-EVs with the immune system cells have recently increased considerably. Moreover, the role of EVs derived from immune cells as modulators of cellular responses has gained attention; in this context, we highlight the role of macrophage-derived EVs in tumor progression (4).

Macrophages are classified into two different subpopulations based their polarization status: M1 (classically activated) and M2 (alternatively activated). These states represent only a portion of the existing subpopulations of macrophages. M1 macrophages are known for their cytotoxic activities against cancer cells whereas M2 macrophages play a role in the elimination of pathogens, angiogenesis, and extracellular matrix remodeling with subsequent tissue repair (5). Since 1970, macrophages have been described within the tumor microenvironment; these cells, known as tumor-associated macrophages (TAM), assemble M2 macrophages, and are capable of promoting tumor growth (6). Recently, many studies have described the importance of TAM-derived EVs (TAM-EVs) in the advancement and progression of gastric, liver, pancreas, and colorectal tumors. This chapter highlights the interaction of EVs released by macrophages in gastrointestinal cancer, as can be observed in Figure 1 and summarized in Table 1.

GASTRIC CANCER

Gastric cancer (GC) is the fifth most common malignant tumor and the fourth cause of cancer-related deaths worldwide (7). The major cause of GC is *Helicobacter pylori* infection, leading to approximately 870,000 new GC cases annually

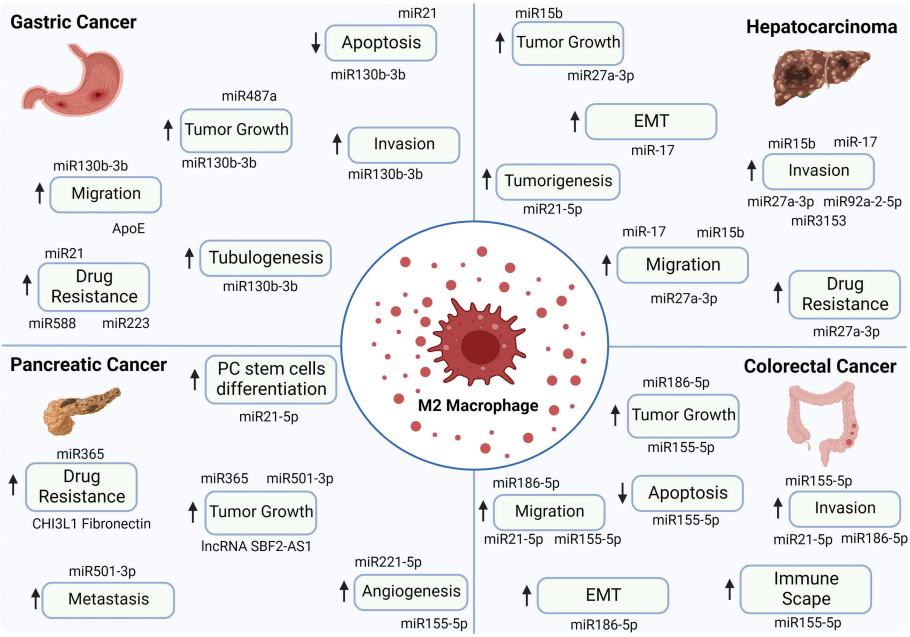

Figure 1. Extracellular vesicles released by macrophages and their effects on gastrointestinal cancers. Created with BioRender.com. EMT, epithelial mesenchymal transition; miR, microRNA, PC, pancreatic cancer.

TABLE 1 Extracellular vesicles released by macrophages and their effects on gastrointestinal cancers

Gastric Cancer				
Vesicle Origin	**Content**	**Effect**	**Mechanisms**	**Reference**
M2 macrophages from THP-1	miR130b-3b	Apoptosis protection; Induces migration, invasion, tubulogenesis, and tumor growth	Suppresses MML3 and GRHL2	(17)
M2 macrophages from RAW 264.7	N.D	Increases TFF2 and GSII Lectin	N.D.	(13)
M2-EV	miR487a	Induces cell proliferation, tumor growth	Inhibits TIA1	(16)

Table continued on following page

TABLE 1 **Extracellular vesicles released by macrophages and their effects on gastrointestinal cancers (*Continued*)**

M2 macrophages from human and murine (C57BL/6) bone marrow monocytes	ApoE	Induces migration	PI3K – AKT	(14)
M2 macrophages	miR21	Decreases gastric cancer cell apoptosis; Drug resistance against Cisplatin	Downregulates PTEN	(21)
M2 macrophages from THP-1	miR223	Drug resistance against doxorubicin	Inhibits FBXW7	(22)
M2 macrophages from murine bone marrow monocytes	miR588	Drug resistance against Cisplatin	Inhibits Cylindromatosis	(23)
M1 macrophages	miR16-5p	Activates T Cell Reduces tumor growth	Downregulates PD-L1	(24)
Pancreatic Cancer				
Vesicle Origin	**Content**	**Effect**	**Mechanism**	**Reference**
M2 macrophages from murine (C57BL/6) bone marrow monocytes	miR155-5p; miR221-5p	Induces angiogenesis	N.D.	(30)
M2 macrophages from THP-1	miR365	Induces tumor growth	Activates BTG2/FAK/AKT	(29)
M2 macrophages from THP-1	miR501-3p	Induces tumor growth and metastasis	Activates TGFB (TGFBR3)	(27)
M2 macrophages from THP-1	miR21-5p	Promotes the differentiation and activity of PC stem cells	Activates KLF3	(31)
M2 macrophages from THP-1	lncRNA SBF2-AS1	Induces tumor growth	Enhances XIAP	(27)

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TABLE 1 **Extracellular vesicles released by macrophages and their effects on gastrointestinal cancers (*Continued*)**

M2 macrophages from THP-1cells	miR365	Drug resistance against Gemcitabine	N.D.	(26)
M2 macrophages	CHI3L1 and fibronectin	Drug resistance against Gemcitabine	Activates ERK	(28)
M1 macrophages from THP-1	N.D.	Reduces Drug resistance against Gemcitabine and Deferasirox	N.D.	(32)
Hepatocarcinoma				
Vesicle origin	**Contente**	**Effect**	**Mechanism**	**Reference**
M2 macrophages from THP-1	miR27a-3p	Induces stemness, proliferation, invasion, migration, tumor growth, and drug resistance in HCC cells;	Downregulates TXNIP	(34)
M2 macrophages	miR17	Increases expression of EMT- related proteins and stemness-related genes; Migration and Invasion	Impairment on TGF-β1/BMP-7	(35)
M2 macrophages from murine bone marrow monocytes	miR21-5p	Increases levels of PD1 and TIM3 on $CD8^+$T cells and higher malignant degree of tumorigenesis in C57/BL6 mice	Activates YOD1/ YAP/β-catenin	(44)

Table continued on following page

TABLE 1 **Extracellular vesicles released by macrophages and their effects on gastrointestinal cancers (*Continued*)**

M2 macrophages from THP-1 polarized in contact to arsenic	miR15b	Increases proliferation, migration, and invasion	Downregulates LATS1 and inhibits Hippo pathway, and growth of HCC xenografts on nude mice	(45)
M2 macrophages from THP-1 polarized in contact with hepatic cancer cells	miR92a-2-5p and miR 3153	Increases invasion	Suppresses AR and PHLPP and increases AKT phosphorylation	(38)
M1 macrophages from THP-1	miR326	Decreases proliferation and colony formation ability and suppression of migration and invasion; Reduces tumor growth.	Inhibits NF-kB	(46)
TAM treated with propofol	miR142-3p	Inhibits invasion	Downregulates RAC1	(47)
Colorectal Cancer				
Vesicle origin	**Contente**	**Effect**	**Mechanism**	**Reference**
M2 macrophages from THP-1	miR186-5p	Induces migration, invasion, and tumor growth, increasing EMT	Downregulates DLC1; Activates	(48)
M2 macrophages from colorectal cancer tissues	miR155-5p miR21-5p	Induces migration and invasion	Downregulates BRG1	(49)
M2 macrophages from colon cancer tissues	miR155-5p	Induces proliferation and Immune escape; Inhibits apoptosis	Downregulates ZC3H12B	(50)

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TABLE 1 **Extracellular vesicles released by macrophages and their effects on gastrointestinal cancers (*Continued*)**

M1 macrophages from MC38 subcutaneous tumor models	TAM-EVs proteins	Induces T cells proliferation and activation of proteins related to immune response, inflammation, cell migration and adhesion, signal transduction, as well as proteins associated with lipidic metabolism and transport	N.D.	(51)
M1 macrophages from RAW 264.7	N.D.	Decreases tumor cell viability	N.D.	(52)

ApoE, apolipoprotein E; AKT, protein kinase B; EMT, epithelial mesenchymal transition; FBXW7, WD repeat domain-containing 7; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; GRHL2, grainyhead-like 2; LATS1, large tumor suppressor kinase 1; miR, microRNA; N.D., not defined; NF-kB, nuclear factor k B. PI3K, phosphoinositide 3-kinases; PHLPP, PH domain leucine-rich repeat-containing protein phosphatase; TAM, tumor-associated macrophage; TGF, tumor growth factor; TIA, T-cell intracellular antigen-1; TXNIP, Thioredoxin-interacting protein; YAP, yes-associated protein 1; XIAP, X-linked inhibitor of apoptosis protein.

worldwide (8, 9). Other risk factors include age, obesity, smoking, and dietary habits (10). Because early stage of GC is asymptomatic, most cases are diagnosed at advanced stages, compromising effective treatment (11). The crosstalk between GC and macrophages occurs via extracellular vesicles, produced from gastric tumor cells and macrophages (12). Macrophages treated with deoxycholic acid release EVs, which in turn increase spasmolytic polypeptide-expressing metaplasia markers (TFF2 and GSII lectin) in gastric organoids, a significant risk factor for GC (13). M2-EVs could be internalized by gastric cancer cells, transferring ApoE, an apolipoprotein expressed in TAM within the tumor microenvironment. Once ApoE is internalized, the PI3K-AKT signaling pathway is activated, promoting tumor cell migration (14).

Several studies have shown the involvement of microRNA (miR)-enriched EV in the initiation, progression, angiogenesis, metastasis, and chemoresistance of GC (15). Yang and colleagues observed that M2 macrophages could induce gastric tumor cell proliferation in an EV-dependent manner (16). The authors observed that the presence of miR487a in M2-EVs targeted the T-cell intracellular antigen-1 (TIA), leading to gastric cancer cell proliferation and tumor growth (16). M2-EVs containing miR130b-3b have the same ability to promote GC growth. Zhang and colleagues showed an increase of miR130b-3b in GC and

gastric tumor cells (17). EVs derived from THP1-differentiated M2 macrophages were rich in miR130b-3b, leading to apoptosis protection, migration, invasion, tubulogenesis, and tumor growth (17). M2-EVs also downregulated MML3 (myeloid/lymphoid or mixed-lineage leukemia 3), which in turn downregulated Grainyhead-like 2 (GRHL2) (17), a tumor suppressor (18). Low expression of MML3 has been implicated in low survival of GC patients (19).

Macrophage-derived EVs, obtained by differentiating U937 cells to macrophages, loaded with miR21 inhibitor induced apoptosis and inhibited migration of gastric tumor cell (20). Corroborating these findings, Zheng and colleagues observed, in vitro and in vivo, that M2-EVs can deliver miR21 to gastric tumor cells (20). The authors also observed that miR21 can downregulate PTEN, leading to suppression of cell apoptosis and PI3K/AKT signaling activation, conferring cisplatin resistance to gastric cancer (21). Additionally, macrophage-derived EVs containing miR223 can confer doxorubicin resistance in GC cells through inhibition of F-box and WD repeat domain-containing 7 (FBXW7). On the other hand, when miR223 were knocked down in macrophages, their M-EVs could not confer doxorubicin resistance in GC (22). Cui and colleagues also observed the role of miR588 in chemoresistance (23). The authors observed that EVs containing miR588 derived from M2 macrophages induced resistance to cisplatin in vitro and in vivo. Furthermore, miR588 targeted cylindromatosis, a deubiquitinating enzyme that counteracts the E3 ubiquitin ligases-mediated protein ubiquitination, which is essential to tumorigenesis (23).

While M2-EVs have a role favoring GC, M1-EVs can act in a counter way. Li and colleagues observed that M1-EVs carrying miR16-5p downregulate PD-L1, allowing T cell immune response, culminating in a reduction of GC progression (24). Thus, M1-EVs could represent an attractive cell-based therapy for GC treatment.

PANCREATIC CANCER

The pancreas is considered an essential organ of the digestive system and has relevant endocrine functions. Malignant tumors that affect this organ have been increasingly reported and studied. Pancreatic tumor types described as malignant can be related to endocrine or non-endocrine functions. Malignant tumors related to non-endocrine functions in the pancreas are the seventh cause of cancer mortality worldwide and are divided into two main classes: pancreatic ductal adenocarcinoma (PDAC), and cystadenocarcinoma. PDAC constitutes about 85% of pancreatic cancers (PC), with approximately 50,000 cases diagnosed yearly (7). Older age, obesity, diabetes mellitus, smoke, and alcohol are some risk factors that may be closely associated with a higher incidence of PC. Conditions such as chronic pancreatitis and family history can also be considered risks for developing this type of cancer. Treatment for patients diagnosed with PDAC are limited, and the survival rate of these patients is extremely low, and more therapeutic interventions need to be studied and described to improve patient survival (25).

The interaction of immune system cells with PC cells is widely described in the literature and is considered a key factor for tumor development and progression. TAM-EVs are already described as critical players in PC progression (26–29). As a

form of communication, immune system cells release EVs, which can affect the metabolism of target tumor cells. It was observed by Yang and colleagues that EVs from PC cells could polarize macrophages to the M2 phenotype, increasing the expression of specific markers for TAM, such as Arginase-1 and CD206 and, in turn, M2 macrophages-derived EVs (M2-EVs) were able to induce angiogenesis in PDAC (30). M2-EVs facilitated neovascularization in murine aortic endothelial cells, and these pro-angiogenic effects were attenuated when exosomes were removed from the conditioned medium of M2 macrophages. EVs also mediated increased migration, proliferation, and invasion by PC cells from macrophages (27, 29, 30).

It is well established that EVs are crucial elements that support communication between biologically active cells, exchanging nucleic acids (circRNA, mRNA, miR), lipids, and proteins, and act on intercellular signaling carrying important information to target cells (2). Several miR such as miR (27), miR365 (26, 29), and miR21-5p (31) have been described as present in M-EVs in PC, as crucial for sustaining PC development (27, 29, 31). Long non-coding RNAs (lncRNAs) present in M-EVs have also been described as a promoter of PC development (PANC-1 cell line). lncRNA SBF2-AS1 downregulation can promote miR122-5p expression and reduce XIAP (X-linked inhibitor of apoptosis protein), limiting PC progression (27). Specific proteins have also been identified by proteomics in PC TAM-EVs, such as chitinase 3-like-1 (CHI3L1) and fibronectin (FN1), which are crucial for chemotherapeutics resistance mechanisms (28). M2-EVs were also able to promote angiogenesis in vivo in nude mice by carrying specific microRNAs to endothelial cells, such as miR155-5p, miR221-5p (30), and miR501-3p (27).

miR365 expression in M-EVs promotes the expression of the same miR in PANC-1 and BxPC3 (tumor cell lines) compared to non-tumor cells and induces resistance to specific drugs used in chemotherapy, such as gemcitabine in a murine model (26) through ERK pathway activation (28); Proliferation, migration, and invasion were increased in tumor cells treated with M2-EVs. Treatment with an exosome generation inhibitor (GW4869) mitigated these effects, suggesting the importance of exosomes for PC development. Specific proteins involved in epithelial-mesenchymal transition (EMT) have been observed in PC cell lines, with increased mesenchymal marker expression such as vimentin and SNAIL and decreased epithelial marker e-cadherin expression; this suggests plasticity, mobility, and invasion induction. When miR365 was silenced in M2-EVs, PC cells malignant behaviors such as proliferation, migration, invasion, expression of apoptotic genes, and EMT markers were attenuated. miR365 suppression has been shown to limit tumor growth in mice and negatively regulate BTG2/FAK/AKT pathway. Thus, overexpression of BTG2 could reverse the pro-tumorigenic effect of M2-EVs in PC (29). Yin and colleagues noted that TAM recruitment in PDAC is highly associated with PC metastasis once TAM infiltrates were observed in tissues of metastatic patients other than healthy patients (27). TAM infiltrate also correlated with increased expression of miR501-3p. M2-EVs also increased PDAC cells migration and invasion in nude mice, promoting tumor formation and metastasis with a significant increase in tumor weight and volume through the TGFβ pathway (TGFβR3 downregulation) (27).

Chang and colleagues observed M2-EVs ability to promote PC stem cell differentiation (via miR21-5p high expression) and sustain cancer development through migration, invasion, and protection from apoptosis by M2-EVs (31). High levels of miR21-5p are considered a critical factor for poor prognosis in PC

patients, so M2-EVs with miR21-5p downregulation were able to decrease tumor stem cells differentiation in vitro and in vivo, decreasing tumors volume and size in an animal model, via KLF3 pathway activation that acts as an important tumor suppressor gene (31).

On the other hand, M1-EVs improved chemotherapeutic response to gemcitabine and deferasirox when delivered to tumor cells inside M1-EVs, decreasing proliferation, migration, and chemoresistance in PC (32). In this way, we highlight the importance of M2-EVs for the development and tumor progression of PC (26–31) and M1-EVs as a possible therapeutic strategy for PC treatment improving chemotherapeutic agents' efficiency as a front line to combat the disease (32).

HEPATOCELLULAR CARCINOMA

Since 1980, liver cancer incidence and death rates have tripled and doubled, respectively (33). This disease was predicted to be the sixth most diagnosed cancer worldwide in 2020, and liver cancer was the third cause of death among cancers, with 830,000 deaths (7). Among primary liver cancers, hepatocellular carcinoma (HCC) is the main pathological type and the most common, accounting for about 80% of the cases (34, 35). HCC has a poor prognosis due to its heterogeneity (35) and limited therapeutic methods, which are often only available for the early stages of cancer (36). Interactions between tumor cells and their microenvironment play a role in its heterogeneity and pathogenesis. More precisely, the interaction between cancer cells and the growth factors and cytokines released by the microenvironment cells can affect their plasticity (37) and promote liver fibrosis, initiation, progression, and metastasis (34, 38).

Even though immune cells have a tumor suppressive role, they can be affected by cancer cells, thus contributing to tumor development. Macrophages, which in the liver are called Kupfer cells, are the most abundant immune cells in this tissue and establish a direct relationship with hepatocytes to maintain homeostasis (39). TAM within the HCC tumor microenvironment promotes cell proliferation, invasion, migration, angiogenesis, and immunosuppression and is often correlated with poor prognoses (40). Besides their capacity to directly transfer cellular lipids and proteins to other cells, macrophages secrete extracellular vesicles affecting neighboring cells.

Li and colleagues have demonstrated that EVs derived from THP-1 cells driven into M2 macrophages increased miR27a-3p in SMMC-7221 HCC cell lines, increasing their proliferation, migration, and invasive capacities (34). In addition, M2-EVs further enriched in miR27a-3p promoted stemness, proliferation, invasion, migration, drug resistance in HCC cells, and accelerated tumor growth in vivo in a nude mice model. According to the authors, these effects on HCC cells were promoted by miR27a-3p-induced TXNIP downregulation (34). Accordingly, it has been demonstrated that TAM-EVs deliver MIR17HG and miR17 to HepG2 HCC cells, leading to an impairment on TGF-β1/BMP-7 pathways, an increased expression of EMT- related proteins and stemness-related genes, and both migratory and invasive capacities. Corroborating, in vivo experiments conducted in mice have demonstrated that the treatment with TAM-derived EVs increased the

expression of ACVR1, ID1, and vimentin and decreased the expression of E-cadherin in M2-scarce tumor xenografts (35).

$CD8^+$T cells-mediated immune response is critical for inhibition of HCC progression. Their dysfunction is one of the main reasons for tumor escape from the immune system, together with the presence of excessive T suppressor cells. When in the condition of prolonged antigen exposure, $CD8^+$T cells undergo exhaustion, weakening their anti-tumoral effect (41–43). Pu and colleagues demonstrated that the injection of HCC cells together with EVs derived from murine bone marrow monocytes differentiated into M2 macrophages promoted a higher malignant degree of tumorigenesis in C57/BL6 mice together with a decrease in the number of $CD8^+$T cells; these were accompanied by increased levels of PD1 and TIM3 on $CD8^+$T cells, and impairment in both their proliferative and killing capacity (44). Straightforward, they have demonstrated the role of the miR21-5p content within EVs on $CD8^+$T cells exhaustion once the inhibition of miR21-5p in EVs partially reverted this effect. The authors have concluded that these effects were mediated by miR21-5p-dependent YOD1 targeting, thus favoring the YAP/β-catenin pathway (44).

It is known that arsenic, an environmental toxicant, causes HCC; recently, it has been demonstrated that when in contact with arsenic, monocytes from THP-1 lineage were polarized towards M2 macrophages and released EVs enriched in miR15b.

When those EVs were transferred to HCC cells, they promoted downregulation of large tumor suppressor kinase 1 (LATS1), thus, inhibiting the Hippo pathway, which is involved in inhibiting the occurrence of metastasis on HCC. Therefore, HCC cells underwent increased proliferation, migration, and invasion. Corroborating those data, EVs from M2-THP-1 macrophages inhibited Hippo signaling, promoting the growth of HCC xenografts on nude mice (45).

When in co-culture with hepatic cancer cells, THP-1 macrophages presented increased expression of the M2 markers: arginase-1, CD163, CD206, and TGF-β; in addition, M-EVs transferred both miR92a-2-5p and miR3153 to HCC cells, resulting in the suppression of both androgen receptor (AR) and PHLPP expression, culminating in AKT phosphorylation and increased invasiveness (38).

On the other hand, studies have demonstrated that M-EVs can suppress HCC cell progression. Bai and colleagues have demonstrated that M1 macrophages derived from THP-1 cells deliver miR326 to HCC cells, reducing their proliferation and colony formation ability and suppressing both migratory and invasive capacities (46). Furthermore, those EVs also promoted HCC cells apoptosis. Authors have concluded that the suppressive roles of miR326 were performed through the inhibition of NF-kB in HCC cells. It is worth mentioning that these results were also observed in vivo; in mice transplanted with HCC cells, the treatment with M1-EVs overexpressing miR326 reduced both tumor volume and weight (46). EVs released by TAM treated with propofol have also demonstrated anti-tumor effects via delivery of miR142-3p to HCC, culminating in RAC1 downregulation, which inhibited cell invasion both in vitro and in vivo (47).

Conversely, it is essential to highlight that transfer of miR from macrophages to hepatic cancer cells is not exclusively dependent on EVs. Aucher and colleagues have demonstrated that the transfer of miR425 and miR122 from human macrophages to hepatic HuH7 HCC cells was only triggered by direct contact, dampening cell proliferation (39).

COLORECTAL CANCER

Colon is the lower region of the intestinal tract, ranging from the caecum to the rectum, having water and salts absorption function from non-digested foods, and elimination of waste products with mass movements (33). Estimates of the GLOBOCAN 2020 showed that colorectal cancer is the third in incidence and the second in the cause of death considering both sexes worldwide (7). The tumor stage strongly influences patients' survival at the time of diagnosis. Data show that colorectal cancer correlate is more common in developed countries (33).

To highlight the importance of macrophages-derived extracellular vesicles in colorectal cancer, Guo and colleagues conducted a study using human colorectal adenocarcinoma cell lines, SW480 and HCT-8, and a human monocyte cell line, THP-1 differentiated to M2 phenotype (48). The study showed that M2-EVs could deliver miR186-5p to cancer cells, being the most abundant microRNA in M2-EVs. miR186-5p performs a pro-tumor function, increasing migration, invasion, and growth of cancer cells, besides negatively regulating the mRNA and protein expression of DLC1, a tumor suppressor gene. This microRNA also induces the β-catenin signaling pathway, associated with the EMT process. Altogether, these results demonstrate that miR186-5p is responsible for promoting the effects of M2-EVs and paves the way for the investigation of other microRNAs delivered to cancer cells within M2-EVs and display a similar pro-tumor effect (48).

Lan and colleagues, using human colon cancer cell lines SW48, SW480 e CO-115, demonstrated that M2-EVs extracted from samples of colorectal cancer patients co-cultivated with colorectal cancer cells could influence tumor biology, allowing the transfer of functional molecules (49). Among these molecules, miR21-5p and miR155-5p are overexpressed in M2-EVs and have protumor action that directly influences migration and invasion of tumor cells. One of these microRNAs targets is BRG1, reducing its expression and involving in tumor metastasis (49). Similarly, Ma and colleagues have shown that M2-EVs from colorectal cancer patients have anti-apoptotic action and demonstrated a new target, ZC3H12B, which is regulated negatively by promoting immune escape through IL6 upregulation in human colon cancer cell lines SW48 e HT29 (50).

Using a subcutaneous tumor model with MC38 cell inoculation in mice, Cianciaruso and colleagues have shown that TAM-EVs derived from this model have an M1 profile, correlated with the increase in survival (51). It was also observed that M1-EVs appear to be able to stimulate T cells. Through proteomic analysis, the study showed that TAM-EVs express 62 proteins related to immune response, inflammation, cell migration, adhesion, and signal transduction, as well as proteins associated with lipid metabolism and transport (51).

The importance of EVs in the biology of colorectal tumors has been proven in recent years, as shown above. However, could EVs be used in the therapeutic field? Veld and colleagues evaluated M1-Like and M2-Like macrophages as photosensitizers carriers of Zinc Phthalocyanine (ZnPc) for photodynamic therapy for cancer treatment (52). The study used the MC38 colon cancer cell line and RAW264.7 mouse monocyte/macrophages. The results showed that EVs could function as drug carriers, with M1 containing ZnPc being capable of reducing MC38 viability showing efficiency for the photodynamic therapy (52).

CONCLUSION

We have compiled how extracellular vesicles released by M2/TAM macrophages are associated with the progression of gastrointestinal cancers, while those from M1 macrophages exert anti-tumoral effects. Furthermore, we highlight two possible strategies for cancer management: blocking the release of M2-EVs or inducing M1-EVs within the tumor microenvironment.

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