The Immuno-Modulation Effect of Macrophage-Derived Extracellular Vesicles in Chronic Inflammatory Diseases

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As natural nanocarriers and intercellular messengers, extracellular vesicles (EVs) control communication among cells. Under physiological and pathological conditions, EVs deliver generic information including proteins and nucleic acids to recipient cells and exert regulatory effects. Macrophages help mediate immune responses, and macrophage-derived EVs may play immunomodulatory roles in the progression of chronic inflammatory diseases. Furthermore, EVs derived from various macrophage phenotypes have different biological functions. In this review, we describe the pathophysiological significance of macrophage-derived extracellular vesicles in the development of chronic inflammatory diseases, including diabetes, cancer, cardiovascular disease, pulmonary disease, and gastrointestinal disease, and the potential applications of these EVs.

Keywords: macrophage-derived extracellular vesicles, immunomodulation, chronic diseases, therapeutic strategy, inflammation

BACKGROUND

Extracellular vesicles (EVs) are natural phospholipid bilayer-derived particles expressing specific surface markers (e.g., tetraspanins, Alix, and TSG101) secreted by cells into the extracellular space (1). EVs have been isolated from various types of cells, tissues, and even bodily fluids (2). They are categorized mainly as exosomes (~40–160 nm diameter), microvesicles, and apoptotic bodies (~50 nm to 1 μm diameter) (3, 4). Initially, EVs were considered waste released by cells (5). More recently, their roles in cell–cell interactions have been identified (6, 7). Various cargos in the form of nucleic acids, proteins, lipids, and metabolites are transferred by EVs to recipient cells, thereby influencing the biological functions of those cells. EVs are highly heterogeneous and dynamic, depending on the parental cell source and microenvironment (3). Due to their unique characteristics and properties, EVs are critical mediators of various physiological and pathological processes including the immune response, cell proliferation and migration, tumor invasion, and metastasis (8–10). Furthermore, they are used as diagnostic tools and as therapeutic delivery systems carrying biological factors and/or drugs (11–13).
Macrophages (Mφ) are derived from monocytes in the bone marrow and are involved in specific and nonspecific immunity of the body. In nonspecific immunity, the biological functions of Mφ include removing dead cells and cellular debris, and presenting antigens for recognition. In specific immunity, activated Mφ have immunomodulatory functions by secreting cytokines. Moreover, they play a major role in antigen presentation and initiation of the immune response (14). Mφ are divided mainly into two phenotypes: classically activated M1 (M1Mφ) and alternatively activated M2 (M2Mφ) (15). Mφ play essential roles in the microenvironment and are also regulated by that microenvironment. Phenotypic polarization of Mφ has a dynamic influence on the balance between inflammation and tissue repair. Moreover, the functions and properties of EVs secreted from Mφ (Mφ-EVs) are influenced by Mφ polarization, with different phenotypes of Mφ-EVs being involved in diverse biological processes under various physiological and pathological conditions (16).

Inflammation is defined biologically as the response of the body’s immune system to a stimulus. Mainly caused by various pathogens and tissue damage, it plays an important role in tissue repair and is considered a protective response of the organism (17). Activated Mφ dominate the histopathology of chronic inflammation and can amplify the inflammatory response by mediating the release of inflammatory mediators (18). In 2010, the WHO stated that chronic diseases such as cardiovascular disease, diabetes, cancer, and chronic respiratory disease account for approximately two-thirds of global deaths (19). To date, several studies have confirmed the link between chronic inflammation and chronic disease, although the exact mechanisms are still not clear (20–22). Inflammation not only plays an important role in host defense mechanisms but also greatly contributes to the pathological process of chronic diseases. Therefore, targeting inflammation is a promising strategy for improving and treating chronic diseases.

In this review, we summarize the crucial role of Mφ-EVs in the pathogenic mechanisms of chronic diseases such as atherosclerosis, diabetes, cancer, lung-related disease, cardiovascular-related disease, and gastrointestinal-related disease. In addition, therapeutic strategies based on Mφ-EVs are discussed, as well as the challenges associated with their application.

**Mφ-EVs**

EVs are vesicles derived from the phospholipid bilayer released by cells (23), including various subtypes of nanoscale-to-microscale particles. They transmit information that helps regulate recipient cells (Table 1). Furthermore, they retain the biological properties of the parental cells (71). Thus, different phenotypes of Mφ-EVs play different roles in different pathological conditions (Figure 1).

However, there is no consensus on the specific markers of EVs subtypes according to the MISEV2018 (23). In this review, we primarily focus on EVs 150 nm or less in size.

**Molecular Components of Mφ-EVs**

The RNA molecules enclosed in Mφ-EVs comprise mainly mRNA (intact mRNA and mRNA fragments) (31, 43), miRNA (60), long non-coding RNA (46), and tRNA (1). Lee et al. obtained EVs from Mφ treated with Shiga toxin 2a toxoids and found that they express higher levels of mRNAs encoding the pro-inflammatory cytokines IL-1β and IL-8, thereby exacerbating inflammation (9). Zhu et al. evaluated the features of Mφ-EVs and EVs derived from tumor-associated Mφ (TAM-EVs) (72) and found that different RNA processing proteins resulted in different RNA profiles. These results indicate that EVs that transport mRNA may be internalized and translated. miRNA incorporated in EVs could circulate in the blood without degradation from blood RNase activity (3). In addition, Mφ-EV miRNAs participate in the immune response (51), induce mesenchymal stem cell differentiation (57), regulate the tumor-associated microenvironment (73, 74), and mediate cell proliferation and migration (52). However, to date, few studies have investigated the presence of DNA in EVs (3).

In recent years, proteomic studies have provided new insights into the protein components of Mφ-EVs. Yao et al. reported a number of differentially expressed proteins in IFN-α-activated Mφ-EVs (35), including 74 upregulated and 20 downregulated proteins involved in antiviral-related pathways. In another study, 22 upregulated proteins in LPS-induced Mφ-EVs activated the NOD-like receptor signaling pathway and the NLRP3 inflammasome in patients with acute liver injury (25). Huang et al. screened proteins from silica-exposed Mφ-EVs and identified 291 differentially expressed proteins; the SPP1 protein was found to play a critical role in the response to silicosis (36). These findings emphasize that the biological functions of EV proteins vary under different conditions.

EVs can also deliver soluble mediators such as cytokines and enzymes. Haque et al. investigated the role of Mφ-EVs exposed to cigarette smoke condensate in HIV patients and found an association with catalase upregulation (29). In colitis patients, EVs transmitting CC chemokine 1 directly interact with CCR8 to alleviate colon damage and relieve inflammation (12).

Lipids also play an important role in the functions of Mφ-EVs. Kadiu et al. applied lipidomic analysis to explore how Mφ-EVs facilitate HIV-I infection (75) and found that MVs and exosomes derived from Mφ have unique lipid profiles. Specifically, viral membranes enriched with lipids, such as glycerophosphoserine, sphingomyelin, and dihydrosphingomyelin, were readily detected in the MV fraction; by contrast, phosphatidylethanolamine/ceramide was identified only in the exosome population (75). However, the complete lipid profiles of Mφ-EVs are poorly understood and require further study.

**Biogenesis of Mφ-EVs**

The mechanisms of microvesicle biogenesis are associated with outward budding and fission of the plasma membrane. Apoptotic bodies are released as blebs in cells undergoing apoptosis (3). The biogenesis of exosomes is a complex and dynamic process. Invagination of the plasma membrane initiates the first step of exosome biogenesis and produces endocytic
TABLE 1 | The cargos transmitted by M2-EVs to recipient cells.

| EVs Source | Precondition of Macrophages | Disease model | Cargos | Mechanism | Reference |
|------------|-----------------------------|---------------|--------|-----------|-----------|
| M2-EVs     | –                           | Hepatocellular carcinoma | Integron αβ1 (CD11b/CD18) | Promote invasive and metastasis of hepatocellular carcinoma cells via activating MMP-9 | (24) |
| M2-EVs     | Induced by LPS              | Acute liver injury | Differentially expressed proteins like IL1α, Gbp2 | Activate the NLRP3 and NOD-like receptor signaling pathway | (25) |
| M2b-EVs    | –                           | Colitis | CCL1 chemokine | Interact with CCR8 to increase IL-6 expression and Treg percentages | (12) |
| M2-EVs     | Treated with endotoxin and nigercin | Autoimmune diseases | The immune response-related proteins | Activate NF-κB signaling pathway | (26) |
| TAM-EVs    | Reprogramed glioblastoma-derived EVs | Glioblastoma | Arginase-1 | Promote tumor growth | (27) |
| M2-EVs     | Stimulated with angiotensin II | Bleomycin-induced lung fibrosis | Angiotensin II type 1 receptor | Promote tumor growth | (28) |
| M2-EVs     | Exposed to cigarette smoke condensate | Silicosis | BIP, XBP1s and P-eIF2α | Induce endoplasmic reticulum stress | (30) |
| M2-EVs     | Exposed to silica           | Diabetic nephropathy | TGF-β1 mRNA | Activate TGF-β1/Smad3 signaling pathways | (31) |
| M2-EVs     | High glucose–treated        | AS | EVs transfer | Attenuate the growth and tube formation of endothelial cells | (32) |
| M2-EVs     | Oxidized LDL–stimulated     | Cells death | Globotriaosylceramide (Gb3), IL-1β and IL-8 mRNAs | Actuate stress-associated MAPKs and induce ER stress in Gb3-expressing cells | (9) |
| M2-EVs     | Treated with Shiga toxin 2a toxoids | – | Integron β1 | Promote internalization of integrin β1 in primary HUVECs, make the internalized integrin β1 accumulate in the perinuclear region and not recycled back to the plasma membrane | (23) |
| M2-EVs     | –                           | Breast adenocarcinoma | Human a disintegrin and metalloproteinase 15 | Enhance binding affinity for integrin αvβ3 in an RGD-dependent manner and suppress vitronectin- and fibronectin-induced cell adhesion, growth, and migration | (34) |
| M2-EVs     | Treated with interferon-α or not | Viral infection | Differentially expressed proteins | Be involved in two of the top biological process categories: “Defense response to virus” and “Type I interferon signaling pathway” | (35) |
| M2-EVs     | Exposed to silica           | Silicosis | SPP1 protein | Phagocytosed by fibroblasts and generate corresponding myofibroblasts | (36) |
| M2-EVs     | –                           | – | Leukotriene B4 | Produce chemotactic eicosanoids and induced granulocyte migration in the present of Ca (2+) ionophore and arachidonic acid | (37) |
| M2-EVs     | Exposed or not to either LPS or to stationary phase of L. mexicana (Leishmania) | Parasite infection (Leishmania) | GP63 | Induce signaling molecules and transcription factors in naive macrophages | (38) |
| M2-EVs     | Exposed to calcium oxalate monohydrate crystals | Kidney stone disease | L-plastin, coronin-like protein, pyruvate kinase, actin-related protein 3, HSP90β, and vimentin | Activate inflammasome, promote monocyte and T-cell migration, monocyte activation and macrophage phagocytic activity | (39) |
| M2-EVs     | –                           | Inflammation brain | Brain derived neurotrophic factor | Interact with brain microvesSEL endothelial cells via the integrin LFA-1 and ICAM-1, the carbohydrate-binding C-type lectin receptors | (40) |
| M2-EVs     | Stimulated with angiotensin II | Hypertension | ICAM-1 and PAI-1, mR-17 | Increase the expression of ICAM1 and PAI-1 in human coronary artery endothelial cells | (41) |
| M2-EVs     | Mock-infected or infected with the macrophage-tropic HIV-1 Bal. strain | HIV | 48 mRNAs (e.g., mR-29a, mR-150) | Unclear | (42) |
| M2a-EVs    | –                           | – | mRNA of Il1b, CCL2, CCL7, CCL3, PI4 | Affect the TLR, TNF, NLR, and NF-κB signaling pathways in recipient cells | (43) |
| M2b-EVs    | –                           | Lung cancer | AGAP-2-AS1 | Strengthen the radioreistance of radioresistant lung cancer cells via upregulating NOTCH2 and downregulating miR-206 | (44) |
| M2-EVs     | –                           | Pancreatic cancer | LncRNA SBF2-AS1 | Suppress tumorigenic ability of pancreatic cancer via repressing miR-122-5p and upregulating XIAP | (45) |

(Continued)
| EVs Source | Precondition of Macrophages | Disease model | Cargos | Mechanism | Reference |
|------------|----------------------------|---------------|--------|-----------|-----------|
| M2-EVs     | –                          | Hypertrophic scar | LncRNA-ASLNCS5088 | Modulate glutaminases expression in fibroblasts via targeting miR-200c-3p | (46) |
| M1-EVs     | –                          | Inflammatory bowel disease | MR-21a-5p | Decrease E-cadherin expression and excessively activate IL-C2 via promoting QATA-3 | (47) |
| M1-EVs     | –                          | Myocardial infarction | MR-155 | Suppress Sirt1/AMPKα2-endothelial nitric oxide synthase and RAC1/PAK2 signaling pathways through targeting RAC1, PAK2, Sirt1, and AMPKα2 | (48) |
| M2-EVs     | Treated with IL-4-          | AS             | MR-99a/146b/378a | Target NF-αB and TNF-α signaling pathways to suppress inflammation | (49) |
| M2-EVs     | –                          | Idiopathic pulmonary fibrosis | MR-142-3p | Decrease the expression of TGFB-R1 and profibrotic genes in alveolar epithelial cells and lung fibroblasts | (50) |
| M2-EVs     | Treated with IL-4-          | AS             | MR-21-3p | Secrete various chemokines and cytokines, activate immune signaling pathways | (51) |
| M2-EVs     | Treated with IL-4-          | AS             | MR-146a | Promote vascular smooth muscle cells proliferation and migration through targeting PTEN | (52) |
| M2-EVs     | Treated with IL-4-          | AS             | MR-144-5p | Increase the release of reactive oxygen species ROS and neutrophil extracellular traps NETs via targeting SOD2 | (53) |
| M2-EVs     | Treated with IL-4-          | AS             | MR-30a-5p | Promote the CD2 expression and suppressed the proliferation of human gastric epithelial cells by targeting FOXD1 | (54) |
| M2-EVs     | Treated with IL-4-          | AS             | MR-103-3p | Target KLF4 to promote the proliferation and activation of hepatic stellate cells | (55) |
| M2-EVs     | Treated with IL-4-          | AS             | MR-146a-5p | Suppress monocyte transendothelial migration and endothelial permeability via targeting JAM-C | (56) |
| M2-EVs     | Treated with IL-4-          | Fracture       | MR-5106 | Induce bone mesenchymal stem cells towards osteoblastic fate by targeting salt-inducible kinase 2 and 3 | (57) |
| M2-EVs     | Treated with IL-4-          | Diabetic fracture | MR-144-5p | Inhibit bone mesenchymal stem cells osteogenesis differentiation by targeting Smad1 | (58) |
| M2-EVs     | Treated with IL-4-          | Type 2 diabetes | MR-210 | Bind with mRNA sequences of NDUFA4 gene to impair glucose uptake and mitochondrial complex IV activity | (59) |
| M2-EVs     | Treated with IL-4-          | Spontaneous abortion | MR-153-3p | Suppress the proliferation and migration of trophoblast cells through the IDO/STAT3 pathway. | (60) |
| M2-EVs     | Treated with IL-4-          | Pulmonary fibrosis | MR-328 | Enhance pulmonary interstitial fibroblast proliferation by targeting FAM13A | (61) |
| M2-EVs     | Treated with IL-4-          | Myocardial infarction | MR-222 | Promote BMSCs apoptosis by targeting Bcl-2 | (62) |
| M2-EVs     | Treated with IL-4-          | Ischemia-reperfusion injury | MR-148a | Suppress the expression of thioredoxin-interacting protein and inactivate the TLR4/NF-αB/NLRP3 signaling pathway | (63) |
| M2-EVs     | Treated with IL-4-          | Ischemia-reperfusion injury | MR-29a | Promote inflammatory cytokines secretion and cardiomycoty pyrosis by targeting MCL-1 | (64) |
| M2-EVs     | Treated with IL-4-          | Type 2 diabetes | MR-29a | Induce insulin resistance through targeting PPARγ signaling | (65) |
| M2-EVs     | Treated with IL-4-          | Carotid artery injuries | MR-222 | Target CDKN1B and CDKN1C to promote vascular smooth muscle cell proliferation and migration | (66) |
| M2-EVs     | Treated with IL-4-          | Acute myocardial infarction | MR-1271-5p | Decrease cardiomycyte apoptosis via decreasing SOX6 expression | (67) |
| M2-EVs     | Activated by Toll-like receptor 3 | Hepatitis C virus infection | MR-29 | Induce the expression of IFN-α and IFN-stimulated genes (ISGs, Mxα, OAS-1, and OAS-2) in human hepatic cells | (68) |
| M2-EVs     | Activated by Toll-like receptor 3 | Breast cancer | MR-130, MR-33 | Perform anti-tumor effect by polarizing M6 from M2 to M1 phenotype | (69) |
| M2-EVs     | Activated by Toll-like receptor 3 | Asthma | MR-370 | Reduce cell apoptosis, relive inflammation in vitro and in vivo through suppressing the FGF1/IL6/STAT3 axis | (70) |
vesicles. The fusion of multiple endocytic vesicles leads to the formation of early endosomes (EEs). Many intercellular cargoes are encapsulated in such EEs in a clathrin- or caveolin-dependent or independent manner (76, 77). With the assistance of the Golgi complex, EEs invaginate and mature into late endosomes known as multivesicular bodies (MVBs) (2). Inward membrane budding results in the formation of intraluminal vesicles (ILVs), which are housed in MVBs (78). MVBs show two types of reversion: they may fuse with the plasma membrane and release ILVs into the extracellular space as exosomes, or they may fuse with lysosomes or autophagosomes and ultimately lead to degradation (4). Endosomal sorting complex required for transport (ESCRT) is the best-described mechanism underlying MVB formation and protein sorting in MVBs (79). ESCRT includes four different protein complexes, ESCRT-0, -I, -II, -III (80). The ESCRT-0, -I and ESCRT-II complexes form a recognition domain in the endosomal membrane that recognizes and ubiquitinates membrane proteins. The ESCRT-III complex is responsible for membrane budding and the release of ILVs (81). Other critical players include Syntenin-1, TSG101, ALIX, Rab GTPases, Pmel17, and tetraspanins (4). In addition to proteins and ceramides, lipids such as sphingomyelinases are also involved in the biogenesis of exosomes (82).

Furthermore, stimulation could influence Mφ-EV cargo sorting or ultimate release in the biogenesis of Mφ-EVs. Mφ exposed to irradiated apoptotic cancer cells activate peroxisome proliferator-activated receptor gamma (PPARγ) and increase the expression of phosphatase and tensin homolog (PTEN) in Mφ-EVs (83). Similarly, Mφ exposed to extracellular adenosine triphosphate (ATP) activate the P2X7 signaling pathway and increase calpain activity, ultimately leading to IL-1β expression and loading of unconventional proteins into Mφ-EVs (84, 85). Interestingly, the more released of Mφ-EVs would result from lipopolysaccharide (LPS) stimulation, and the mechanism is related to upregulation of Rab27a and Rab27b, while it is inhibited by IL-25 (86).

**Relationship Between Mφ and Mφ-EVs**

The description of the Mφ phenotype is widely accepted: classically activated or inflammatory M1Mφ are induced by IFN-γ, TNF-α or bacterial LPS, whereas alternatively activated or anti-inflammatory M2Mφ are polarized by IL-4 and IL-13 (87, 88). Plasticity is an important property of Mφ (89). Cytokines in the microenvironment can alter the phenotype of Mφ (90). Different phenotypes have different functions; for example, M1Mφ secrete higher levels of pro-inflammatory cytokines, exerting potent antimicrobial and antitumor activities that
impair tissue regeneration and wound healing (91–93). By contrast, M2Mφ have anti-inflammatory effects that remove debris and apoptotic cells, promote angiogenesis, and facilitate fibrosis, tissue repair, and wound healing (94–96).

There are three major phenotypes of Mφ-EVs: unpolarized M0Mφ-derived EVs (M0-EVs), M1Mφ-derived EVs (M1-EVs), and M2Mφ-derived EVs (M2-EVs) (97). Their biological functions vary depending on the parental cell properties. For instance, in the pathogenesis of atherosclerosis (AS), M1-EVs containing a high level of miR-155 suppress the proliferation of fibroblasts and promote the development of AS (98), while M2-EVs deliver miR-1271-5p to suppress cardiomyocyte apoptosis and perform cardiac repair (67). Moradi-Chaleshtori et al. reported that M1-EVs polarize Mφ from the M2 to M1 phenotype and have antitumor effects by carrying miR-130 and miR-33 (69). M2-EVs promote cell invasion in breast cancer by transporting miR-223 to target the Me2ζ/β-catenin pathway (99). Furthermore, each EV phenotype has polarization-specific control in the bone repair process. M0-EVs and M2-EVs enhance bone regeneration, while M1-EVs inhibit bone repair (100).

**IMMUNOMODULATORY EFFECTS OF Mφ-EVs in Chronic Inflammatory Disease**

Inflammation is the body’s defense response to stimuli such as infection or injury, and it can be divided into acute and chronic phases. Acute inflammation is rapid in onset and short in duration, mainly characterized by exudative lesions. Chronic inflammation can lead to pathological changes in tissues and organs, which in turn cause diverse chronic diseases, including diabetes, cancer, cardiovascular disease, respiratory disease, and gastrointestinal disease (101, 102).

Chronic diseases are driven by pathological inflammation, eventually leading to tissue damage (103). In short, disorders resulting from inflammation-related pathways are the primary mechanism leading to chronic disease.

EVs play a vital role in maintaining tissue homeostasis and regulating disease progression as another mode of cellular interaction (104, 105). Numerous studies have elucidated the impact of Mφ-EVs on chronic inflammation and disease. EVs derived from different Mφ have unique effects under various pathological conditions (106, 107) (Figure 2).

**Cardiovascular Disease**

AS plays a prominent role in coronary heart disease, cerebral infarction, and peripheral vascular disease (108). It is a multifactorial disease, and its exact pathogenesis has not been elucidated. Hypertension, hyperlipidemia, obesity, smoking, and diabetes are all risk factors for its development (109). AS is characterized by lesions in affected arteries starting from the intima, with lesions involving mainly large and medium arteries. It can lead to deposits of lipids and complex sugars, hemorrhage, thrombus formation, and many other conditions that eventually thicken and stiffen the arterial wall and narrow the vessel lumen. AS plaques are composed primarily of immune, foam, and inflamed smooth muscle cells (110).

AS is an inflammatory response caused by the retention of cholesterol-rich, B-type lipoproteins in susceptible areas of medium and large arteries (111). Dysregulation of the balance between cellular and systemic cholesterol promotes the deposition of such lipoproteins in the arterial wall (109).

The development of AS is closely associated with endothelial cell damage, vascular inflammation, and massive accumulation of Mφ. The imbalance between Mφ recruited to plaques and Mφ migration from plaques to regional lymph nodes causes deposition of lipid-laden Mφ in the arterial wall, further promoting the inflammatory progression of AS. Thus, Mφ migration regulates the development of AS (108, 112). EVs mediate intercellular communication in atherosclerotic plaques (113). Furthermore, activated monocytes or Mφ-EVs can propagate inflammatory signals and modulate AS development via various pathways (114–116). Nguyen et al. reported that EVs secreted from Mφ loaded with oxidized low density lipoprotein are taken up by naïve Mφ and inhibit Mφ migration in vitro and in vivo (116). In addition, Mφ-EVs can block the migration of Mφ to the chemokine stimulator CCL2, and EVs transport miR-146a, which suppresses the expression of genes in Mφ related to cell migration, such as HuR and IGF2BP1 (116). Mφ may also promote the progression of AS via activation of the NF-kB pathway. The modulatory effect of Mφ-EVs on AS is further evidenced by their ability to regulate hematopoietic stem cells differentiation and necrosis by suppressing the TNF-α/NF-kB signaling pathway (49). Furthermore, Zhu et al. isolated EVs from nicotine-treated Mφ and illustrated that they aggravate the development of AS by transporting the exosomal miR-21-3p target PTEN, which enhances vascular smooth muscle cell migration and proliferation (52).

Oxidative stress and inflammation are closely related, and they form a feed-forward loop that promotes the development of AS. During AS, Mφ produce significant levels of reactive oxygen species (ROS) via mitochondrial metabolism (109). M1Mφ enhance aerobic glycolysis and reduce mitochondrial activity. In contrast, M2Mφ mediate mitochondrial oxidative phosphorylation (117). Bouchareychas et al. isolated EVs from mouse bone marrow-derived Mφ treated with IL-4 and applied these EVs to naïve BMDMs, which resulted in enhanced ATP production and cellular respiration. These results indicate that EVs can effectively regulate cellular reprogramming by improving energy metabolism (49). Mφ-derived EVs treated with superoxide dismutase 2, a target of oxidized low density lipoprotein, showed increased ROS production and the release of neutrphil extracellular traps via miR-146a (53).

Mφ modulation plays an essential role in immunomodulatory processes during cardiac repair and in remodeling post-myocardial infarction (118). Hypoxia/serum deprivation-induced M1-EVs transport miR-222, which promotes apoptosis and inhibits viability in bone marrow mesenchymal stem cells by targeting B-cell lymphoma-2 (62). miR-155 is predominantly expressed in Mφ and cardiac fibroblasts and is
one of the most abundant miRNAs in M1-EVs (119). The expression of miR-155 is upregulated in M1-EVs from the hearts of mice after acute myocardial infarction (AMI). EVs enriched with miR-155 inhibit the proliferation of fibroblasts and promote the inflammatory response; a deficiency of miR-155 decreases the incidence of cardiac rupture after AMI and improves cardiac function (98). Previous studies have observed angiogenesis-inhibiting effects of M1-MPs, but the mechanism of action is not entirely understood (120). M1-EVs transfer miR-155 to endothelial cells, reducing their angiogenic ability by downregulating miR-155 target genes including RAC1, PAK2, Sirt1, and AMPKα2 (48). Thus, inhibition of miR-155 expression may be a novel method for the clinical treatment of MI. By contrast, M2-EVs transport miR-1271-5p, which suppresses apoptosis in cardiomyocytes and performs a cardiac repair function in AMI by targeting SOX6 (67).

Generally, ischemia–reperfusion is applied to restore coronary artery blood flow and relieve disease progression. However, numerous studies have demonstrated that ischemia–reperfusion injury (IRI) can lead to cardiac dysfunction due to calcium overload and overproduction of free radicals such as ROS (121). Induction of hypoxia–reoxygenation is the main method for establishing IRI in animal models (64). Wang et al. demonstrated that Mϕ subjected to hypoxia–reoxygenation are polarized toward M1-Mϕ and derived EV miR-29a to promote cardiomyocyte pyroptosis by targeting myeloid cell leukemia-1

FIGURE 2 | The Immuno-modulation Effect of Mϕ-EVs in chronic inflammatory diseases. Mϕ-EVs regulate the immune response and cell proliferation and migration and are involved in signaling pathways in the development of chronic inflammatory disease. Mϕ-EVs, Macrophage-derived extracellular vesicles; Th2, CD4+ T helper 2 lymphocytes; AKT, Protein kinase B; GS, Glycogen synthase; TNF-α, Tumor necrosis factor alpha; NF-κB, Nuclear factor κ-light-chain-enhancer of activated B cells; IGF2BP1, Insulin-like growth factor 2 mRNA-binding protein 1; HuR, Human antigen R; ROS, Reactive oxygen species; RAC1, RAS-related C3 botulinum toxin substrate 1; PAK2, p21-activated kinase 2; Sirt1, Sirtuin 1; AMPKα2, Adenosine monophosphate-activated protein kinase alpha 2; TRAF6, TNF receptor associated factor 6; MMP2, Matrix metalloproteinase 2; CD90, Cluster of differentiation 90; ST8MAR, Phosphorlymphin tation 90; JUNB, AP-1 transcription factor; IGF-1R, Insulin-like growth factor receptor; mTOR, Mammalian target of rapamycin; CDK6, Cyclin-dependent kinase 6; PI3K, Phosphatidylinositol-3-kinase; TERF1, Telomeric repeat binding factor 1; CDA, Cytidine deaminase; BRG1, Brahma-related gene 1; TGFβ, TGF-beta type III receptor; STAT3, Signal Transducers and Activators of Transcription 3; Treg, Regulatory T lymphocytes; CDK6, Cyclin-dependent kinase 6; PI3K, Phosphatidylinositol-3-kinase; TERF1, Telomeric repeat binding factor 1; CDA, Cytidine deaminase; BRG1, Brahma-related gene 1; TGFβ, TGF-beta type III receptor; STAT3, Signal Transducers and Activators of Transcription 3; Treg, Regulatory T lymphocytes; CDK6, Cyclin-dependent kinase 6; PI3K, Phosphatidylinositol-3-kinase; TERF1, Telomeric repeat binding factor 1; CDA, Cytidine deaminase; BRG1, Brahma-related gene 1; TGFβ, TGF-beta type III receptor; STAT3, Signal Transducers and Activators of Transcription 3; Treg, Regulatory T lymphocytes; CDK6, Cyclin-dependent kinase 6; PI3K, Phosphatidylinositol-3-kinase; TERF1, Telomeric repeat binding factor 1; CDA, Cytidine deaminase.
inhibitory effects of insulin on glucose production (128). EVs, suppresses the expression of PPAR
Moreover, miR-155, which is overexpressed in obese ATM-
restricted insulin secretion by targeting the SIRT2 gene and
fl
Similarly, miR-29a within ATM-EVs promotes obesity-induced
proliferation and migration of endothelial cells and
release of pro-inflammatory cytokines responsible for IR. MØ in normal adipose tissue express CD206 receptors and release Arg-1, but those in inflamed tissues are polarized to the M1 phenotype (127). In a previous study, administering EVs derived from adipose tissue MØ (ATM-EVs) from obese mice to lean mice caused glucose intolerance and IR, while administering lean mice ATM-EVs to obese mice improved glucose tolerance and insulin sensitivity (128).

Chronic low-grade inflammation is the main cause of IR, leading to islet β cell failure. Qian et al. analyzed the effects on β cells of M1-EVs and EVs isolated from islet-resident MØ from mice fed a high-fat diet (129) and found that miR-212-5p restricted insulin secretion by targeting the SIRT2 gene and regulating the Akt/GSK-3β/β-catenin pathway (129). Moreover, miR-155, which is overexpressed in obese ATM-EVs, suppresses the expression of PPARγ and impairs the inhibitory effects of insulin on glucose production (128). Similarly, miR-29a within ATM-EVs promotes obesity-induced IR by directly targeting PPARγ (65).

Many complications can occur during the late stages of diabetes. The persistence of diabetic inflammation activates inflammatory cells, which secrete immunomodulatory cytokines (130). A common complication of diabetes is difficult healing. MØ-EVs show a remarkable decrease in the release of pro-inflammatory cytokines, enhancing the proliferation and migration of endothelial cells and accelerating wound healing via their anti-inflammatory effects (131). Similar research has shown that M1-EVs can regulate MØ phenotypic reprogramming, repolarizing M1MØ to M2MØ, which in turn promotes wound healing (132). Bone homeostasis is also disturbed by diabetes mellitus. Zhang et al. isolated EVs from diabetic bone marrow-derived MØ and found that they transport miR-144-5p, which inhibits osteogenesis differentiation by targeting Smad1 and suppressing facture repair in vivo (58). Diabetic nephropathy is a peripheral small artery occlusive disease caused by diabetic neuropathy and lower extremity vasculopathy. M2-EVs that transport miR-25-3p may alleviate podocyte injury induced by high glucose levels by activating autophagy of the cells through suppression of DUSP1 expression (133). Zhu et al. found that Mø-derived EVs treated with high levels of glucose might activate glomerular mesangial cells through the TGF-β1/Smad3 pathway, promote proliferation, and induce the production of fibrotic and inflammatory factors (31). Similarly, high-glucose-treated Mø-derived EVs induce overexpression of inflammatory cytokines and activate NF-κB p65 signaling pathways (134). ATM-EVs contain high levels of miR-210, and miR-210 in ATM-EVs has been shown to regulate glucose uptake and mitochondrial chain complex IV activity by targeting NDUFA4 gene expression, which promotes the pathogenesis of diabetes (59).

These findings highlight the importance of Mø-EVs in adipose tissue and suggest that the contents and functions of ATM-EVs vary with the ATM phenotype.

**Cancer**
Cancer is the leading cause of death worldwide (135). In 2012, approximately 14.1 million new cancer cases and 8.2 million cancer deaths were recorded worldwide (135). Furthermore, with the aging population, the incidence and mortality rate of cancer have rapidly been increasing, imposing a significant burden on society. Inflammation plays a crucial role in the development of cancer (136). The “seed and soil” theory proposed in 1889 (137) compares cancer cells to seeds and the human microenvironment to soil and postulates that whether a tumor metastasizes depends on whether the soil meets the growth conditions of the seed (137). In recent years, more studies have focused on the regulatory roles of active immune cells such as MØ, neutrophils, and mast cells in the tumor microenvironment (TME) (138, 139). Among such cells, TAMs play the most critical role in the TME (140, 141).

Mø-EVs have diverse effects on the TME under various pathological conditions (4, 142, 143). For example, EVs transport apolipoproteins from TAMs to gastric cancer cells to promote cell migration (144), the expression of matrix metalloproteinase-2, and the pathogenesis of abdominal aortic aneurysms by activating the JNK and p38 signaling pathways (145).

EVs mediate intercellular communication in the TME via miRNA-induced epigenetic modifications in recipient cells. EVs miRNAs can regulate tumor cell migration, invasion, and drug resistance via various mechanisms, which in turn affect tumorigenesis (Table 2).

In recent years, proteomics has dramatically facilitated the study of proteomic profiles of EVs, and research on Mø-EVs has provided new insights into how the TME is regulated (161, 162). A thorough comparative proteomic analysis of EVs revealed that TAM-derived exosomal proteins are responsible mainly for RNA processing and proteolytic functions and determined that recipient cells have an improved capacity to degrade denatured or misfolded proteins after uptake of TAM-EVs, which enhances their survival in the TME (72). Furthermore, TAM-EVs have molecular profiles associated with Th1/M1 polarization profiles; they enhance inflammation and immune responses and promote the proliferation and activation of T cells ex vivo. Thus, TAM-EVs are potent stimulators of antitumor immunity (163). They also activate the matrix metalloproteinase-9 signaling pathway to...
TABLE 2 | The biological functions of Mφ-EV miRNAs in TME.

| EVs sources | Disease model | MiRNAs | Mechanism | Reference |
|-------------|---------------|--------|-----------|-----------|
| M1-EVs      | Breast cancer cells | MIR-130, MIR-33 | Perform anti-tumor effect by polarizing macrophage from M2 to M1 phenotype | (69) |
| M2-EVs      | Colorectal cancer | MIR-21-5p, MIR-155-5p | Downregulate BRG1 expression, enhance colorectal cancer cells migration and invasion | (107) |
| M2-EVs      | GC             | MIR-21 | Suppress cell apoptosis and strengthen activation of PI3K/AKT signaling pathway via down-regulation of PTEN | (148) |
| TAMs-EVs    | PDAC           | MIR-501-3p | Promote the PDAC cells invasion, migration and tube formation through the downregulation by activating the TGF-β signaling pathway to downregulate TGFBR3 | (147) |
| TAMs-EVs    | Prostate cancer | MIR-95 | Downregulate the downstream gene, JunB, to promote PCa cell proliferation, invasion, and epithelial-mesenchymal transition | (148) |
| M2-EVs      | EOC            | MIR-221-3p | Suppress CDKN1B to enhance the proliferation and G1/S transition of EOC cells | (73) |
| M2-EVs      | EOC            | MIR-223 | Induce cell drug resistance by activating PTEN-PI3K/AKT pathway | (149) |
| TWEAK-stimulated macrophages-EVs | EOC | MIR-7 | Inhibition of tumor metastasis and aggressiveness in vitro and in vivo by EGFR/AKT/ERK1/2 signaling pathway | (150) |
| TAMs-EVs    | EOC            | MIR-146b-5p | Inhibit the HUVECs migration by activating TRAF6/NF-κB/MMP2 pathway. | (151) |
| TAMs-EVs    | EOC            | MIR-29a-3p, MIR-21-5p | Suppress STAT3 expression and regulate the ratio of Treg/Th17 | (152) |
| M2-EVs      | Breast cancer cells | MIR-223 | Target the Met2c-β-catenin pathway and promote breast cancer cell invasion | (99) |
| M2-EVs      | HCC            | MIR-142, MIR-223 | Inhibit HCC proliferation through suppressing STMN1 and IGF-1R expression | (153) |
| TAMs-EVs    | HCC            | MIR-125a/b | Suppress cell proliferation and stem cell properties by targeting CD90 | (154) |
| TAMs-EVs    | HCC            | MIR-92a-2-5p | Suppress androgen receptor translation, modify the PHLPp/p-AKT/β-catenin signaling to increase liver cancer cells invasion | (74) |
| M2-EVs      | PDAC           | MIR-149-5p | Promote the invasion and migration of HCC by increasing MMP9 pathway | (155) |
| TAMs-EVs    | PDAC           | MIR-365 | Uregulate pyrimidine metabolism and increase NTP levels in cancer cells, upregulating CDA to promote gemcitabine resistance | (156) |
| TAMs-EVs    | Neuroblastoma cells | MIR-155 | Downregulate TERF1 expression to increase CDDP resistance both in vitro and in vivo | (157) |
| M2-EVs      | Bladder cancer | MIR-21 | Promote migration, proliferation and invasion, suppress apoptosis of glioma cells by reducing PEG3 expression | (158) |
| M2-EVs      | Bladder cancer | MIR-21 | Promote cell migration and induce cell CDDP resistance | (159) |
| M2-EVs      | Esophageal Cancer | MIR-26a | Regulate the impacts of overexpressed AFAP1-AS1 on cell migration and invasion | (160) |

GC, Gastric cancer; PDAC, Pancreatic ductal adenocarcinoma; EOC, Epithelial ovarian cancers; HCC, Hepatocellular carcinoma; PI3K, Phosphatidylinositol-3-kinase; AKT, Protein kinase B; PTEN, Phosphatase and tensin homolog; TGFBR3, TGF-beta type III receptor; JUNB, AP-1 transcription factor; CDKN1B, Cyclin-dependent kinase inhibitor 1B; EGFR, Epidermal growth factor receptor; ERK1/2, Extracellular signal-regulated kinase 1/2; TRAF6, TNF receptor associated factor 6; MMP2, Matrix metalloproteinase 2; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; STAT3, Signal Transducers and Activators of Transcription 3; Treg, regulatory T-lymphocytes; Th17, IL-17-producing CD4+ T-lymphocytes; STMN1, Stathmin 1; IGF-1R, Insulin-like growth factor receptor; CD90, Cluster of differentiation 96; PHLPp, PH domain leucine-rich-protein phosphatase; p-AKT, Phosphorylated-Akt; MMP9, Matrix metallopeptidase 9; CDA, Cytidine deaminase; CDDP, Cisplatin; PEG3, Paternally expressed gene 3; TERF1, Telomeric repeat binding factor 1; Mef2c, Myocyte enhancer factor; AFAP1-AS1, Actin filament associated protein 1 antisense RNA.

Promote hepatocellular carcinoma tumor migration by mediating the intercellular transfer of αMβ2 (CD11b/CD18) (24).

Recently, it was found that EVs contain damaged DNA from the nucleus and mitochondria, regulating tumor immunity via paracrine and activated cytoplasmic DNA sensor pathways and in specific immune cell subpopulations (164). After chemotherapy, exposing Mφ to apoptotic breast cancer cells causes higher levels of IL-6 to be released and delivered to cancer cells via increased phosphorylation of STAT3, promoting the proliferation and metastasis of the cells (8). Furthermore, Mφ-EVs may synthesize proteins such as thromboxane and thromboxane B2 (163). However, it is unclear whether they contain functional endogenous DNA. In oral squamous cell carcinoma, THP-1-derived EVs and native human Mφ-derived EVs have been shown to activate the AKT/GSK-3β signaling pathway, reducing the proliferative effects of 5-FU and cis-diaminedichloroplatinum (CDDP) and the apoptosis of OSC-4 cells (165).

Metabolic reprogramming, an essential hallmark of malignancy, is regulated by the microenvironment. TAM-derived EVs enhance aerobic metastasis and the anti-apoptotic ability of carcinoma cells by transporting a myeloid-specific long non-coding RNA and HIF-1α-stabilizing long non-coding RNA (HISLA) (166). HILSA inhibits the hydroxylation and degradation of HIF-1α, whereas carboxylic acid secreted from growing glycolytic cells upregulates HISLA in TAMs, constituting a feed-forward loop between TAMs and growing cells. Thus, HISLA inhibits metastasis and chemoresistance in carcinoma in vivo (166). This suggests that EVs-mediated metabolic reprogramming plays an important role in the intercellular communication between immune and tumor cells. Azambuja et al. proposed that glioblastoma-derived EVs reprogram M1Mφ into TAMs and promote the pro-tumor...
functions of M2Mφ, while these GEV-reprogrammed TAM-EVs promote glioblastoma cell migration and proliferation (27).

In summary, because Mφ are sensitive to microenvironmental stimuli, the composition of their secreted EVs in different disease models change as the Mφ themselves are altered.

Pulmonary Disease
Idiopathic pulmonary fibrosis (IPF) is an intermittent and chronic fibrotic lung disease associated with inflammatory immune damage, caused primarily by chronic alveolar epithelial injury and dysregulated wound healing due to abnormal proliferation of fibroblasts (167). The expression of miR-142-3p is markedly increased in the sputum and plasma of IPF patients, and Mφ-EVs reduce the expression of TGFβ receptor 1 by transporting miR-142-3p, suppressing the progression of pulmonary fibrosis (50). Antifibrotic miRNA delivery in the lung can effectively prevent pulmonary fibrosis and provide new therapeutic avenues for the treatment of IPF. In addition, M2-EVs may transport miR-328, facilitating the proliferation of pulmonary interstitial fibroblasts via family with sequence similarity 13, member A (61).

Another pulmonary fibrosis-related disease is silicosis, which is caused by long-term inhalation of large amounts of free silica dust and is characterized by extensive nodular fibrosis of the lungs (168). EVs have been isolated from silica-exposed Mφ and found to induce the proliferation of myofibroblasts and fibroblasts and increase their expression levels of SPP1 (36). They also induce the overproduction of proinflammatory cytokines and promote myofibroblast activation in an endoplasmic reticulum stress-dependent manner (30).

In acute lung injury, Mφ-EVs in alveolar lavage fluid release various pro-inflammatory factors mainly during the early stages of damage; this activates neutrophils to produce IL-10, which might be responsible for polarizing Mφ to M2c, leading to post-acute lung injury fibrosis (169).

Asthma, a chronic respiratory disease, is characterized by inflammation and hyperresponsiveness of the airways (170). M2-EVs deliver miR-370 to reduce cell apoptosis and relieve inflammation by suppressing the FGF1/MAPK/STAT1 axis (70). M2-EVs have also been found to upregulate AGAP2-AS1 and NOTCH2 expression and downregulate miR-296 expression to strengthen the radioreistance of lung cancer cells (44).

Gastrointestinal Disease
Chronic inflammation influences the development of spasmolytic polypeptide-expressing metaplasia (171), and deoxycholic acid (DCA) enhances the expression of enteral metaplasia markers (172). Xu et al. cocultured mouse stomach organoids with DCA treated macrophage-derived EVs(DCA-Mφ-EVs), and the data revealed that the expression of SPEM marker proteins TFF2, GSI1, SPEM-related ciston Wdcl, Olfm4 and Cflr were considerably inflated when 72h cocultured (172). In addition, miR-30a-5p enriched in Mφ-EVs derived from DCA promotes intestinal metaplasia and inhibits the proliferation of human gastric cancer cells by targeting forkhead box D1 (54). These results suggest that Mφ-EVs may mediate intercellular communication in the DCA microenvironment and promote the progression of spasmolytic polypeptide-expressing metaplasia, providing a new target for treating gastric intestinal metaplasia.

Chronic intestinal inflammation may eventually lead to inflammatory bowel disease (173). To assess the effects of Mφ-derived EVs on inflammatory bowel disease, Yang et al. isolated EVs from the M2aMφ, M2bMφ, and M2cMφ phenotypes and established a dextran sulfate sodium-induced colitis model in mice (12). Treating the mice with M2-EVs improved colon length. Furthermore, compared with EVs derived from M2aMφ and M2cMφ, M2bMφ-derived EVs were more effective. These EVs may interact with CCR8 by releasing the CCL1 chemokine, thereby increasing the expression of IL-4 and number of regulatory T cells to promote the Th2 immune response (12).

POTENTIAL THERAPEUTIC STRATEGIES
EVs are considered a promising tool for immunotherapy, drug delivery, and targeted therapy. Furthermore, some strategies were proposed to strengthen the therapeutic capabilities and broaden the applications of EVs. Recent applications are discussed below (Table 3).

Mφ-EVs as a Drug Candidate
As messengers carrying genes, proteins, and other biomolecules, EVs mediate communication in cells and have therapeutic functions. Kang et al. (25) applied M0-EVs, M1-EVs, and M2-EVs to rat calvaria defects; M2-EVs carrying miR-378a increased the expression of the mesenchymal stem cell osteoinductive genes BMP2 and BMP9 in the bone repair process to promote bone regeneration (100). Furthermore, proteomic profiling analysis of the protein composition of LPS-treated Mφ-EVs (L-Mφ-EVs) revealed that among 341 upregulated proteins in L-Mφ-EVs, 22 are involved in the NOD-like receptor signaling pathway. After L-Mφ-EVs were taken up by hepatocytes, NLRP3 was activated, which promoted acute liver injury (25). In ischemic stroke, microglia are converted into M1 phenotypes that release pro-inflammatory mediators, promoting neuronal apoptosis and brain injury (174). L-Mφ-EVs suppress inflammation, enhance microglial M2 polarization (which induces neuroprotection), and reduce the brain infarct volume in vivo after ischemic stroke (174). The miRNAs in Mφ-EVs are involved in different pathways to regulate the development of disease(Qian et al.; 7, 133). In chronic liver disease, L-Mφ-EVs have been shown to promote the proliferation and activation of hepatic stellate cells by enriching miR-103-3p and targeting Krüppel-like factor 4 (55). IL-4-treated Mφ-EVs transported anti-inflammatory miR-99a/146b/378a to inhibit inflammation by targeting NF-kB and TNF-α signaling, leading to delayed development of AS (49).

In addition, Mφ-EVs may have therapeutic functions via Mφ reprogramming. For example, M2-EVs promote wound healing by enhancing proliferation, angiogenesis, and collagen deposition (132), which suggests that Mφ phenotype reprogramming could provide valuable therapeutic options for the treatment of inflammation-related diseases. M1-EVs can also potentially be used to repolarize M2 to M1Mφ that secrete pro-inflammatory cytokines, have antitumor effects, and decrease tumor growth (175). Similarly,
M1-EVs transport miR-130 and miR-33 to exert antitumor effects in breast cancer by polarizing Mφ from the M2 to M1 phenotype (69).

### Mφ-EVs as Drug-Delivery Systems

Many nanocarrier delivery systems have been designed to improve the efficacy of drugs, and EVs have the following advantages compared with other nanocarrier delivery systems: they transport a variety of endogenous biomolecules, and they are biocompatible, naturally targeted, and small enough to escape the clearance effect of the mononuclear phagocyte system (191, 192). Kanchanapally et al. (176) obtained EVs from different cells, including pancreatic cancer cells, pancreatic stellate cells, and Mφ loaded with doxorubicin (DOX), and compared their antitumor effects. Mφ-EVs loaded with DOX showed the highest antitumor efficiency followed by pancreatic stellate and pancreatic cancer cells. Zhang et al. isolated EVs from mononuclear M1Mφ and M2Mφ from umbilical cord blood and loaded them with CDDP; compared with the M2-EVs, M1-EVs showed increased cytotoxicity in drug-resistant A2780/DDP cells, suggesting that M1-EVs are a potential drug carrier in drug-resistant microenvironments (177).

The inability to cross the blood brain barrier (BBB) limits the application of 98% of therapeutic agents used for the treatment of

| EVs Source | Precondition of Macrophages | EVs Treatment | Disease model | Application | Reference |
|------------|-----------------------------|--------------|---------------|-------------|-----------|
| M1-EVs Induced by LPS | – | – | Colorectal cancer | Enhance the anti-tumor effect of checkpoint inhibitors (anti-PD-L1 antibody) in cancer therapy | (175) |
| M1-EVs Induced by LPS | – | Loaded with Doxorubicin | Pancreatic cancer | Deliver Doxorubicin to perform anti-tumor efficacy | (176) |
| M1-EVs Induced by LPS | – | Loaded with CDDP | Ovarian cancer | Increase cytotoxicity in drug-resistant by loaded with CDDP | (177) |
| M1-EVs Induced by LPS | – | Loaded with Catalase | Inflammation brain | Deliver the brain derived neurotrophic factor to the brain | (40) |
| M1-EVs Induced by LPS | – | Loaded with Edaravone | Parkinson's disease | Deliver catalase to oxidative stress, decrease brain inflammation and increase neuronal survival | (183) |
| M1-EVs Induced by LPS | – | Loaded with Baicalin | Stroke | Improve the bioavailability of Edaravone and strengthen the neuroprotective effects | (13) |
| M1-EVs Induced by LPS | – | Loaded with PTX | Ischemic stroke | Improve the solubility of Baicalin, brain targeting ability and present neuroprotection | (181) |
| M1-EVs Induced by LPS | – | Loaded with Berberine | Lung carcinoma | Deliver PTX to overcome multiple drug resistance and assess anti-cancer therapy | (182) |
| M1-EVs Induced by LPS | – | Engeneered with AA-PEG vector moiety | Pulmonary metastases | Improve the loading capacity and therapeutic effects | (184) |
| M1-EVs Induced by LPS | – | Modified with anti-CD47 and anti-SIPPs | Acidic tumor microenvironment | Target tumors more effectively, reprogram M2Mφ to M1Mφ, exert anti-tumor function | (185) |
| M1-EVs Induced by LPS | – | Loaded with Biomimetic silibinin | Alzheimer’s disease | Inhibit astrocytes activation and alleviate astrocyte inflammation-mediated neuronal damage | (186) |
| M1-EVs Induced by LPS | – | Loaded with Doxorubicin | Triple-negative breast cancer | Co-deliver cholesterol-modified miRNA and chemotherapeutic drugs, perform more specific and robust targeting properties, and suppress tumor growth | (187) |
| M1-EVs Induced by LPS | – | Coated with poly (lactic-co-glycolic acid) | Triple-negative breast cancer | Improve the tumor-targeting, the cellular uptaking and the antitumor efficacy | (188) |
| M1-EVs Induced by LPS | – | Modified with hexyl-5-amidovinyl hydrochloride | AS | Enhance the anti-inflammatory effect and relieve AS | (189) |

PTX, paclitaxel; AS, Atherosclerosis; AA-PEG, Aminoethylamisamide-polyethylene glycol; CDDP, Cisplatin; DC, Dendritic cells.
CNS-related disorders (193). Recently, Yuan et al. (40) discovered that Mφ-EVs can cross the BBB and move into brain microvessel endothelial cells via integrin white corpuscle function-associated matter 1, living thing adhesion molecule 1, and carbohydrate-binding C-type glycoprotein receptors. That study further confirmed that intravenously injected Mφ-EVs crossed the BBB and transported brain-derived neurotrophic factor to the brain (40).

A novel EVs-based formulation for catalase delivery in Parkinson’s disease patients was found to have neuroprotective effects against oxidative stress by inactivating ROS, decreasing brain inflammation, and increasing neuronal survival in vivo (180). That study provided a new theoretical basis for the development of other EVs-based drug-delivery systems for the treatment of CNS diseases, as well as an experimental basis for the in-depth study of the mechanisms involved in EV passage through the BBB. Silibinin, an antioxidant with poor brain targeting, has been applied to improve behavior and cognition in Parkinson’s patients. Huo et al. loaded Mφ-EVs with silibinin to improve its targeting capacity and released the silibinin to suppress astrocyte activation and relieve neuronal damage after crossing the BBB (186). Edaravone (Edv) delays neuronal death caused by acute cerebral infarction. Li et al. (13) prepared Mφ-EVs loaded with Edv, applied them to a rat model with permanent middle cerebral artery occlusion, and found that they notably improved bioavailability and prolonged the half-life of Edv. In addition, using these Edv-loaded Mφ-EVs, it was easier to target Edv to the ischemic side, and the treatment decreased neuronal death and promoted microglia M2 polarization in vivo.

Spinal cord injury severely damages the CNS. Gao et al. (183) developed an M2-EV-loaded berberine drug-delivery system that effectively prolonged the duration of berberine and improved its targeting capacity. In addition, it had anti-inflammatory and anti-apoptotic effects by repolarizing Mφ from the M1 to M2 phenotype. Mφ-EVs loaded with baicalin have been found to ameliorate the solubility and brain-targeting ability of baicalin, leading to significant neuroprotection in patients with ischemic stroke (181).

**Application of Engineered Mφ-EVs**

Through genetic and chemical modifications, engineered EVs can enhance EVs targeting and therapeutic effects in cancer treatment (194). For example, Mφ loaded with paclitaxel show significant loading capacity, sustainable drug release, a profound capacity for accumulation in resistant cancer cells, and high cytotoxicity (182). Mφ loaded with paclitaxel and aminoethylbenzamide-polyethylene glycol readily accumulate in cancer cells and have a higher therapeutic effect in vivo compared with non-vectorized Mφ loaded with paclitaxel (184). M1-EVs tagged with anti-CD47 and anti-SIRPα using a pH-sensitive linker effectively target tumors, block SIRPα and CD47, and reprogram M2Mφ to M1Mφ, thereby exerting antitumor functions (185). Gong et al. stimulated THP-1 cells with phorbol 12-myristate 13-acetate to generate target-specific A15 EVs, packing Dox into them to codeliver cholesterol-modified miRNAs and chemotherapeutic drugs into triple-negative breast cancer cells; the system showed specific and robust targeting capabilities and suppressed tumor growth in vivo (187). To improve triple-negative breast cancer targetability, Li et al. (188) modified the surface of Mφ-EVs with a peptide to target mesenchymal–epithelial transition factor and developed a Mφ-EV-coated poly (lactic-co-glycolic acid) nanoplatform, which improved the efficiency of cellular uptake and the antitumor effects of DOX. Wu et al. (189) electroporated M2-EVs with FDA-approved hexyl 5-aminolevulinate hydrochloride, which produced anti-inflammatory carbon monoxide and bilirubin and further enhanced the anti-inflammatory effect by binding to surface-expressed chemokine receptors and releasing anti-inflammatory cytokines; they also relieved AS.

Modification of EVs may enhance their release of anticancer drugs and their antitumor effects by releasing pro-inflammatory Th1 cytokines. For example, M1-EV nano-formulation-loaded paclitaxel creates a pro-inflammatory environment that improves antitumor activity via the caspase-3 signaling pathway and exhibits antitumor effects in vivo (190).

In summary, Mφ-EVs have similar targeting and regulatory abilities as those of Mφ. Thus, the advantages of Mφ-EVs in terms of their nanometer size, cellular targeting, and low immunogenicity make them excellent candidates for next-generation drug-delivery systems.

**CONCLUSION AND PERSPECTIVES**

There are some unresolved issues regarding Mφ-EVs, such as the efficiency of their isolation and purification (195). To address this, Jang et al. (196) created bioinspired exosome-mimetic nanovesicles by breaking down monocytes or Mφ and found that they had similar functional properties as EVs, with 100-fold better isolation and purification efficiency; they also induced TNF-α-stimulated endothelial cell death and showed antitumor activity in vivo. Choo et al. (175) prepared exosome-mimetic nanovesicles derived from M1Mφ, which effectively repolarized M2Mφ to M1Mφ and promoted the antitumor efficacy of programmed death ligand 1. EVs have been characterized based on protein content (23, 197). However, the molecular hallmarks specifically distinguishing each EV subtype remain unclear (23). This issue should be further explored and addressed.

Overall, studies have shown that Mφ-EV-based immunomodulation strategies are effective treatments for various pathological conditions. In the future, more studies are needed to further investigate Mφ-EV-related mechanisms and develop Mφ-EVs based on therapeutic strategies.

**AUTHOR CONTRIBUTIONS**

QY and YHZ initiated the project, made suggestions and revised the article. XY searched the database and wrote the first draft of the manuscript. XS, YD, MW, and YMZ revised and finalized the manuscript. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Liu J, Wu F, Zhou H. Macrophage-Derived Exosomes in Cancers: Biogenesis, Functions and Therapeutic Applications. *ImmunoLett* (2020) 227:102–8. doi: 10.1016/j.imlet.2020.08.003

2. Wu P, Zhang B, Ocansey DKW, Xu W, Qian H. Extracellular Vesicles: A Bright Star of Nanomedicine. *Biomaterials* (2021) 269:120467. doi: 10.1016/j.biomaterials.2020.120467

3. Yanez-Mo M, Siljander PR, Andreu Z, Zavec AB, Borràs SF, Buzas EI, et al. Biological Properties of Extracellular Vesicles and Their Physiological Functions. *J Extracell Vesicles* (2015) 4:27066. doi: 10.3402/jev.v4.27066

4. Kalluri R, LeBleu VS. The Biology, Function, and Biomedical Applications of Exosomes. *Science* (2020) 367(6478):eaau6977. doi: 10.1126/science.aau6977

5. Pan BT, Teng K, Wu C, Adam M, Johnstone RM. Electron Microscopic Evidence for Externalization of the Transferin Receptor in Vescicular Form in Sheep Reticulocytes. *J Cell Biol* (1985) 101(3):942–8. doi: 10.1083/jcb.101.3.942

6. Liu Y, Wang Y, Lv Q, Li X. Exosomes: From Garbage Bins to Translational Medicine. *Int J Pharm* (2020) 583:119333. doi: 10.1016/j.ijpharm.2020.119333

7. Shi ZY, Yang XX, Malichewe C, Li YS, Guo XL. Exosomal microRNAs-Mediated Intercellular Communication and Exosome-Based Cancer Treatment. *Int J Biol Macromol* (2020) 158:530–41. doi: 10.1016/j.ijbiomac.2020.04.228

8. Yu X, Zhang Q, Zhang X, Han Q, Li H, Mao Y, et al. Exosomes From Macrophages Exposed to Apoptotic Breast Cancer Cells Promote Breast Cancer Proliferation and Metastasis. *J Cancer* (2019) 10(13):2892–906. doi: 10.7150/jca.31241

9. Lee KS, Lee J, Lee P, Kim CU, Kim DJ, Jeong YJ, et al. Exosomes Released From Shiga Toxin 2a-Treated Human Macrophages Modulate Inflammatory Responses and Induce Cell Death in Toxin Receptor Expressing Human Cells. *Cell Microbiol* (2020) 22(11):e13249. doi: 10.1111/cmi.13249

10. Zheng PM, Gao HJ, Li J, Zhang P, Li G. [Effect of Exosome-Derived miR-223 From Macrophages on the Metastasis of Gastric Cancer Cells]. *Zhonghua Yi Xue Za Zhi* (2020) 100(22):1750–5. doi: 10.3761/cma.j.cjbb.20200425.01309

11. Lin J, Li J, Huang R, Liu J, Chen X, Chen XM, et al. Exosomes: Novel Biomarkers for Clinical Diagnosis. *ScientificWorldJournal* (2015) 2015:657086. doi: 10.1155/2015/657086

12. Yang R, Liao Y, Wang L, He P, Hu Y, Yuan D, et al. Exosomes Derived From M2b Macrophages Attenuate DSS-Induced Colitis. *Front Immunol* (2019) 10:2346. doi: 10.3389/fimmu.2019.02346

13. Li F, Zhao L, Shi Y, Liang J. Edaravone-Loaded Macrophage-Derived Exosomes Enhance Neuroprotection in the Rat Permanent Middle Cerebral Artery Occlusion Model of Stroke. *Mol Pharm* (2020) 17(9):3192–201. doi: 10.1021/acs.molpharmaceut.0c00245

14. Porcuna J, MenAñÃ©ndez-Gutiérrez OR, Ricote M. Molecular Control of Tissue-Resident Macrophage Identity by Nuclear Receptors. *Curr Opin Pharmacol* (2020) 53:27–34. doi: 10.1016/j.coph.2020.04.001

15. Orecchioni M, Ghosheh Y, Pramod AB, Ley K. Macrophage Polarization: Different Gene Signatures in M1(LPS+) vs. Classically and M2(LPS-) vs. Alternatively Activated Macrophages. *Front Immunol* (2019) 10:1084. doi: 10.3389/fimmu.2019.01084

16. Shapouri-Moghadam A, Mohammadian S, Vazini H, Taghadosi M, Esmaeili SA, Mardani F, et al. Macrophage Plasticity, Polarization, and Function in Health and Disease. *J Cell Physiol* (2018) 233(9):6425–40. doi: 10.1002/jcp.26429

17. Yu C, Bhatia M, Tang SC, Zhang M, Steiner T. Mediators of Inflammation: Inflammation in Cancer, Chronic Diseases, and Wound Healing. *Mediators Inflamm* (2015) 2015:570653. doi: 10.1155/2015/570653

18. Schotendief D, Beebe-Dimmer J. Chronic Inflammation: A Common and Important Factor in the Pathogenesis of Neoplasia. *CA Cancer J Clin* (2006) 56(2):69–83. doi: 10.3322/canjclin.56.2.69

19. Bazer UE, Buss PA, Goodman RA, Bowman BA. Prevention of Chronic Disease in the 21st Century: Eliminating of the Leading Preventable Causes of Premature Death and Disability in the USA. *Lancet* (2014) 384(9937):45–52. doi: 10.1016/s0140-6736(14)60648-6
38. Hassan K, Olivier M. Immunomodulatory Impact of Leishmania-Induced Macrophage Exosomes: A Comparative Proteomic and Functional Analysis. *PloS Negl Trop Dis* (2022) 16(7):e0072185. doi: 10.1371/journal.pntd.0072185

39. Singhto N, Kanlaya R, Nishiyama M, Tanaka M, Yamaguchi T, et al. Macrophage-Derived Exosomes Induce Inflammatory Factors in Endothelial Cells Under Hypertensive Conditions. *Hypertens Res* (2017) 40(4):353–60. doi: 10.1080/1110986X.2016.163

40. Roth WW, Huang MB, Addae-Konadu K, Powell MD, Bond VC. Micro RNA in Exosomes From HIV-Infected Macrophages. *Int J Environ Res Public Health* (2015) 13(1):i13010032. doi: 10.3390/ijerph.13010032

41. Osada-Oka M, Shiota M, Izumi Y, Nishiyama M, Tanaka M, Yamaguchi T, et al. Roles of Extracellular Traps to Drive Atherosclerosis. *Atherosclerosis* (2019) 30(12):4132–39. doi: 10.1016/j.atherosclerosis.2014.04.029

42. Yue Y, Huang S, Wu Z, Wang K, Li H, Hou J, et al. Characterization of mRNA Profiles of Exosomes From Different Forms of Macrophages. *BioMed Res Int* (2020) 2020:1585306. doi: 10.1155/2020/1585306

43. Zhang F, Sang Y, Chen D, Wang X, Yang W, et al. Macrophage-Derived Exosomal Long non-Coding RNA AGAP2-AS1 Enhances Radiotherapy Immunity in Lung Cancer by Reducing microRNA-296 and Elevating NOTCH2. *Cell Death Dis* (2021) 12(5):467. doi: 10.1038/s41419-021-03700-0

44. Zhang YG, Song Y, Guo XL, Miao RY, Fu YQ, Miao CF, et al. Exosomes From M2 Macrophages Carrying miR-148a to Alleviate Myocardial Ischemia/Reperfusion Injury. *Exp Mol Med* (2019) 51(6):1–16. doi: 10.1038/s12276-019-0255-x

45. Yi Q, Zhu T, Zhang T, Wang X, Li W, Chen D, et al. M1 Macrophage-Derived Exosomes Transfer miR-222 to Induce Bone Marrow Mesenchymal Stem Cell Apoptosis. *Lab Invest* (2021) 101(10):1318–26. doi: 10.3384/j.1544-1370.2021.00622-5

46. Yi D, Wang S, Sang S, Ren D, Shali S, Li C, et al. Macrophage-Derived Exosomes Carry microRNA-148a to Alleviate Myocardial Ischemia/Reperfusion Injury via Inhibiting TNXIP and the TLRA/NF-κB/NLRP3 Inflammasome Signaling Pathway. *J Mol Cell Cardiol* (2020) 142:65–79. doi: 10.1016/j.jmcc.2020.02.007

47. Yang W, Qu Z, Yuan J, Li C, Zhao R, Liu W, et al. Hypoxia-Reoxygenation Induces Macrophage Polarization and Causes the Release of Exosomal miR-29a to Mediate Cardiomyocyte Pyroptosis. *In Vitro Cell Dev Biol Anim* (2021) 57(1):30–41. doi: 10.1007/s11626-020-00052-8

48. Liu T, Sun YC, Cheng P, Shao HG. Adipose Tissue Macrophage-Derived Exosomal miR-29a Regulates Obesity-Associated Insulin Resistance. *Biochem Biophys Res Commun* (2019) 513(2):352–58. doi: 10.1016/j.bbrc.2019.07.011

49. Wang Z, Zhu H, Shi H, Zhao H, Gao R, Weng X, et al. Exosomes Derived From M1 Macrophages Aggravate Neointimal Hyperplasia Following Carotid Artery Injuries in Mice Through medR. *Cells Permeability and Monocyte Transendothelial Migration by Targeting Smad1. J Immunol* (2019) 2020:1585306. doi: 10.1155/2020/1585306

50. Xing et al. Immuno-Modulation Effect of M2-MVs.
113. Chistiakov DA, Orekhov AN, Bohrshyev YV. Extracellular Vesicles and Atherosclerotic Disease. *Cell Mol Life Sci* (2015) 72(14):2697–708. doi: 10.1007/s00018-015-1966-2

114. Hoyer FF, Giesen MK, Nunes FranÅsa C, LÃ¡stjohnn D, Nickeng G, Werner N. Monocytic Microparticles Promote Atherogenesis by Modulating Inflammatory Cells in Mice. *J Cell Mol Med* (2012) 16(11):2777–88. doi: 10.1111/j.1365-4934.2012.01595.x

115. Ismail N, Wang Y, Dakhlallah D, Moldovan L, Agarwal K, Batte K, et al. Macrophage Microvesicles Induce Macrophage Differentiation and miR-223 Transfer. *Blood* (2013) 121(6):984–95. doi: 10.1182/blood-2011-08-374793

116. Van den Bossche J, Baardman J, Otto NA, van der Velden S, Neele AE, et al. Mitochondrial Dysfunction Prevents Repolarization of Inflammatory Macrophages. *Cell Rep* (2016) 17(3):684–96. doi: 10.1016/j.celrep.2016.09.008

117. van der Vorst EPC, Weber C. Novel Features of Monocytes and Macrophages in Cardiovascular Biology and Disease. *Arterioscler Thromb Vasc Biol* (2019) 39(2):e30–7. doi: 10.1161/ATVBAHA.118.312002

118. Van den Bossche J, Baardman J, Otto NA, van der Velden S, Neele AE, et al. Mitochondrial Dysfunction Prevents Repolarization of Inflammatory Macrophages. *Cell Rep* (2016) 17(3):684–96. doi: 10.1016/j.celrep.2016.09.008

119. Jablonski KA, Gaudet AD, Amici SA, Popovich PG, Guerau-de-Arellano M. Macrophages, Cytokines and Beta-Cell Death in Type 2 Diabetes. *Biochem Soc Trans* (2008) 36(Pt 3):340–2. doi: 10.1042/bst0360340

120. Zhao T, Wu S, Sui L, Huang Q, Nan Y, Liu J, et al. Reactive Oxygen Species-Based Nanomaterials for the Treatment of Myocardial Ischemia Reperfusion Injuries. *Bioact Mater* (2022) 7:47–72. doi: 10.1016/j.bioactmat.2021.06.006

121. Johnson AM, Olefsky JM. The Origins and Drivers of Insulin Resistance. *Cell* (2013) 152(4):673–84. doi: 10.1016/j.cell.2013.01.041

122. Zeyer M, Stulig T, Adipose Tissue Macrophages. *Immuno Lett* (2007) 112(2):61–7. doi: 10.1016/j.imlet.2007.07.003

123. Ying W, Ropel M, Bandyopadhyay G, Dong Y, Birmingham A, Seo JB, et al. Adipose Tissue Macrophage-Derived Exosomal miRNAs Can Modulate InÂ Vivo and InÂ Vitro Insulin Sensitivity. *Cell* (2017) 171(2):372–384.e12. doi: 10.1016/j.cell.2017.08.035

124. Chen H, Yang Y, Zhang N, Wang J, Sun P, Yang N, et al. Macrophage-Derived Exosomes Impair Beta Cell Insulin Secretion via miR-212-5p by Targeting SIRT2 and Inhibiting Akt/GSK-3Î² Signaling Pathway In Vivo and In Vivo. *Int Immunopharmacol* (2020) 84:106551. doi: 10.1016/j.intimp.2020.106551

125. Yin Z, Ma T, Huang B, Lin L, Zhou Y, Yan J, et al. Macrophage-Derived Exosomes in Abdominal Aortic Aneurysms Development. *J Exp Clin Cancer Res* (2017) 36(1):53. doi: 10.1186/s13046-017-0528-y

126. Jiao Z, Li S, Huang Q, Zhang X, Zhao J, et al. Macrophage-Derived Exosomal microRNA-501-3p Promotes Progression of Pancreatic Ductal Adenocarcinoma Through the TGFBR3-Mediated TGF-Î² Signaling Pathway. *J Exp Clin Cancer Res* (2018) 37(1):310. doi: 10.1186/s13046-019-1313-x

127. Feng R, Peng S, Fang F, Mao L, Chen Z, Yang S, et al. Macrophage-Derived Exosomes Promote Prostate Cancer Progression via Exosome-Mediated miR-95 Transfer. *J Cell Physiol* (2020) 235(12):7972–4. doi: 10.1002/jcpp.29784

128. Zhou X, Shen H, Yin X, Yang M, Wei H, Chen Q, et al. Macrophage-Derived Exosomes Deliver mir-223 to Epithelial Ovarian Cancer Cells to Elicit a Chemoresistant Phenotype. *J Exp Clin Cancer Res* (2019) 38(1):81. doi: 10.1186/s13046-019-1095-1

129. Hu Y, Li D, Wu A, Qiu X, Di W, Huang L, et al. TWEAK-Stimulated Macrophages Inhibit Metastasis of Epithelial Ovarian Cancer via Exosomal Shuttling of microRNA. *Cancer Lett* (2017) 393:60–7. doi: 10.1016/j.canlet.2017.02.009

130. Wu Q, Wu X, Ying X, Zhu Q, Wang X, Jiang L, et al. TWEAK-Stimulated Macrophages Transfer miRNAs That Induce a Treg/Th17 Cell Imbalance in Epithelial Ovarian Cancer. *Cancer Immunol Res* (2018) 6(12):1578–92. doi: 10.1158/2326-6066.cir-17-0479.
Aucher A, Rudnicka D, Davis DM. MicroRNAs Transfer From Human Macrophages to Hepato-Carcinoma Cells and Inhibit Proliferation. J Immunol (2013) 191(12):6250–60. doi: 10.4049/jimmunol.1301728.

Wang Y, Wang B, Xiao S, Li Y, Chen Q. miR-125a/B Inhibits Tumor-Associated Macrophages Mediated in Cancer Stem Cells of Hepatocellular Carcinoma by Targeting CD90. J Cell Biochem (2019) 129(3):3046–55. doi: 10.1002/jcb.27436.

Liu G, Yin L, Ouyang X, Zeng K, Xiao Y, Li Y. M2 Macrophages Promote HCC Cells Invasion and Migration via miR-149-Sp/MMP9 Signaling. J Cancer (2020) 11(5):1277–87. doi: 10.7150/jca.35444.

Binenbaum Y, Fridman E, Yaari Z, Milman N, Schroeder A, Ben David G, et al. Transfer of miRNA in Macrophage-Derived Exosomes Induces Drug Resistance in Pancreatic Adenocarcinoma. Cancer Res (2018) 78(18):5287–99. doi: 10.1158/0008-5472.can-18-0124.

Challagundla KB, Wise PM, Nejadian P, Chava H, Murtadha M, Xu T, et al. Binenbaum Y, Fridman E, Yaari Z, Milman N, Schroeder A, Ben David G, et al. Transfer of miRNA in Macrophage-Derived Exosomes Induces Drug Resistance in Pancreatic Adenocarcinoma. Cancer Res (2018) 78(18):5287–99. doi: 10.1158/0008-5472.can-18-0124.

Wang Y, Wang B, Xiao S, Li Y, Chen Q. miR-125a/B Inhibits Tumor-Associated Macrophages Mediated in Cancer Stem Cells of Hepatocellular Carcinoma by Targeting CD90. J Cell Biochem (2019) 129(3):3046–55. doi: 10.1002/jcb.27436.

Liu G, Yin L, Ouyang X, Zeng K, Xiao Y, Li Y. M2 Macrophages Promote HCC Cells Invasion and Migration via miR-149-Sp/MMP9 Signaling. J Cancer (2020) 11(5):1277–87. doi: 10.7150/jca.35444.

Binenbaum Y, Fridman E, Yaari Z, Milman N, Schroeder A, Ben David G, et al. Transfer of miRNA in Macrophage-Derived Exosomes Induces Drug Resistance in Pancreatic Adenocarcinoma. Cancer Res (2018) 78(18):5287–99. doi: 10.1158/0008-5472.can-18-0124.

Challagundla KB, Wise PM, Nejadian P, Chava H, Murtadha M, Xu T, et al. Binenbaum Y, Fridman E, Yaari Z, Milman N, Schroeder A, Ben David G, et al. Transfer of miRNA in Macrophage-Derived Exosomes Induces Drug Resistance in Pancreatic Adenocarcinoma. Cancer Res (2018) 78(18):5287–99. doi: 10.1158/0008-5472.can-18-0124.

Wang Y, Wang B, Xiao S, Li Y, Chen Q. miR-125a/B Inhibits Tumor-Associated Macrophages Mediated in Cancer Stem Cells of Hepatocellular Carcinoma by Targeting CD90. J Cell Biochem (2019) 129(3):3046–55. doi: 10.1002/jcb.27436.

Liu G, Yin L, Ouyang X, Zeng K, Xiao Y, Li Y. M2 Macrophages Promote HCC Cells Invasion and Migration via miR-149-Sp/MMP9 Signaling. J Cancer (2020) 11(5):1277–87. doi: 10.7150/jca.35444.

Binenbaum Y, Fridman E, Yaari Z, Milman N, Schroeder A, Ben David G, et al. Transfer of miRNA in Macrophage-Derived Exosomes Induces Drug Resistance in Pancreatic Adenocarcinoma. Cancer Res (2018) 78(18):5287–99. doi: 10.1158/0008-5472.can-18-0124.

Challagundla KB, Wise PM, Nejadian P, Chava H, Murtadha M, Xu T, et al. Binenbaum Y, Fridman E, Yaari Z, Milman N, Schroeder A, Ben David G, et al. Transfer of miRNA in Macrophage-Derived Exosomes Induces Drug Resistance in Pancreatic Adenocarcinoma. Cancer Res (2018) 78(18):5287–99. doi: 10.1158/0008-5472.can-18-0124.

Wang Y, Wang B, Xiao S, Li Y, Chen Q. miR-125a/B Inhibits Tumor-Associated Macrophages Mediated in Cancer Stem Cells of Hepatocellular Carcinoma by Targeting CD90. J Cell Biochem (2019) 129(3):3046–55. doi: 10.1002/jcb.27436.

Liu G, Yin L, Ouyang X, Zeng K, Xiao Y, Li Y. M2 Macrophages Promote HCC Cells Invasion and Migration via miR-149-Sp/MMP9 Signaling. J Cancer (2020) 11(5):1277–87. doi: 10.7150/jca.35444.

Binenbaum Y, Fridman E, Yaari Z, Milman N, Schroeder A, Ben David G, et al. Transfer of miRNA in Macrophage-Derived Exosomes Induces Drug Resistance in Pancreatic Adenocarcinoma. Cancer Res (2018) 78(18):5287–99. doi: 10.1158/0008-5472.can-18-0124.

Challagundla KB, Wise PM, Nejadian P, Chava H, Murtadha M, Xu T, et al. Binenbaum Y, Fridman E, Yaari Z, Milman N, Schroeder A, Ben David G, et al. Transfer of miRNA in Macrophage-Derived Exosomes Induces Drug Resistance in Pancreatic Adenocarcinoma. Cancer Res (2018) 78(18):5287–99. doi: 10.1158/0008-5472.can-18-0124.

Wang Y, Wang B, Xiao S, Li Y, Chen Q. miR-125a/B Inhibits Tumor-Associated Macrophages Mediated in Cancer Stem Cells of Hepatocellular Carcinoma by Targeting CD90. J Cell Biochem (2019) 129(3):3046–55. doi: 10.1002/jcb.27436.

Liu G, Yin L, Ouyang X, Zeng K, Xiao Y, Li Y. M2 Macrophages Promote HCC Cells Invasion and Migration via miR-149-Sp/MMP9 Signaling. J Cancer (2020) 11(5):1277–87. doi: 10.7150/jca.35444.

Binenbaum Y, Fridman E, Yaari Z, Milman N, Schroeder A, Ben David G, et al. Transfer of miRNA in Macrophage-Derived Exosomes Induces Drug Resistance in Pancreatic Adenocarcinoma. Cancer Res (2018) 78(18):5287–99. doi: 10.1158/0008-5472.can-18-0124.

Challagundla KB, Wise PM, Nejadian P, Chava H, Murtadha M, Xu T, et al. Binenbaum Y, Fridman E, Yaari Z, Milman N, Schroeder A, Ben David G, et al. Transfer of miRNA in Macrophage-Derived Exosomes Induces Drug Resistance in Pancreatic Adenocarcinoma. Cancer Res (2018) 78(18):5287–99. doi: 10.1158/0008-5472.can-18-0124.
and Intrinsic Heme Biosynthesis for Atherosclerosis Treatment. Angew Chem Int Ed Engl (2020) 59(10):4068–74. doi: 10.1002/anie.201915700
190. Wang P, Wang H, Huang Q, Peng C, Yao L, Chen H, et al. Exosomes From M1-Polarized Macrophages Enhance Paclitaxel Antitumor Activity by Activating Macrophages-Mediated Inflammation. Theranostics (2019) 9 (6):1714–27. doi: 10.7150/thno.30716
191. Lai RC, Yeo RW, Tan KH, Lim SK. Exosomes for Drug Delivery - a Novel Application for the Mesenchymal Stem Cell. Biotechnol Adv (2013) 31 (5):543–51. doi: 10.1016/j.biotechadv.2012.08.008
192. Tran TH, Mattheolabakis G, Aldawsari H, Amiji M. Exosomes as Nanocarriers for Immunotherapy of Cancer and Inflammatory Diseases. Clin Immunol (2015) 160(1):46–58. doi: 10.1016/j.clim.2015.03.021
193. Partridge WM. Drug Transport Across the Blood-Brain Barrier. J Cereb Blood Flow Metab (2012) 32(11):1959–72. doi: 10.1038/jcbfm.2012.126
194. Luan X, Sansanaphongparicha K, Myers I, Chen H, Yuan H, Sun D. Engineering Exosomes as Refined Biological Nanoplatforms for Drug Delivery. Acta Pharmacol Sin (2017) 38(6):754–63. doi: 10.1038/aps.2017.12
195. Zhao X, Zhao Y, Sun X, Xing Y, Wang X, Yang Q. Immunomodulation of MSCs and MSC-Derived Extracellular Vesicles in Osteoarthritis. Front Bioeng Biotechnol (2020) 8:575057. doi: 10.3389/fbioe.2020.575057
196. Jang SC, Kim OY, Yoon CM, Choi DS, Roh TY, Park J, et al. Bioinspired Exosome-Mimetic Nanovehicles for Targeted Delivery of Chemotherapeutics to Malignant Tumors. ACS Nano (2013) 7(9):7698–710. doi: 10.1021/nn402232g
197. Latvall J, Hill AF, Hochberg F, Buzás EI, Di Vizio D, Gardiner C, et al. Minimal Experimental Requirements for Definition of Extracellular Vesicles and Their Functions: A Position Statement From the International Society for Extracellular Vesicles. J Extracell Vesicles (2014) 3:26913. doi: 10.3402/jerv.v3.26913

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