Key role of exosomes derived from M2 macrophages in maintaining cancer cell stemness (Review)

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Abstract. Cancer stem cells (CSCs) constitute a specific subset of cells found within tumors that are responsible for initiating, advancing and resisting traditional cancer treatments. M2 macrophages, also known as alternatively activated macrophages, contribute to the development and progression of cancer through their involvement in promoting angiogenesis, suppressing the immune system, supporting tumor growth and facilitating metastasis. Exosomes, tiny vesicles released by cells, play a crucial role in intercellular communications and have been shown to be associated with cancer development and progression by influencing the immune response; thus, they may serve as markers for diagnosis and prognosis. Currently, investigating the impact of exosomes derived from M2 macrophages on the maintenance of CSCs is a crucial area of research with the aim of developing novel therapeutic strategies to target this process and improve outcomes for individuals with cancer. Understanding the biological functions of exosomes derived from M2 macrophages and their involvement in cancer may lead to the formulation of novel diagnostic tools and treatments for this disease. By targeting M2 macrophages and the exosomes they secrete, promising prospects emerge for cancer treatment, given their substantial contribution to cancer development and progression. Further research is required to fully grasp the intricate interactions between CSCs, M2 macrophages and exosomes in cancer, and to identify fresh targets for cancer therapy. The present review explores the pivotal roles played by exosomes derived from M2 cells in maintaining the stem-like properties of cancer cells.

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Contents

1. Introduction

Cancer stem cells (CSCs) constitute a distinct set of cells found within a tumor that share similar properties to normal stem cells (1). These cells are important for cancer development and progression, as well as in making tumors resistant to chemotherapy and radiation therapy (2). CSCs exhibit self-renewal potential and can differentiate into various cell types found within the tumor, allowing them to continually regenerate the tumor and form more aggressive tumors, even after initial treatment has been administered. They have been identified in various types of cancers, including glioma, breast cancer, lung carcinoma, and leukemia (3-5). Due to their resistance to conventional cancer treatments, they are considered to be one of the contributing factors for tumor recurrence following treatment (3-5).

The CSC niche, similar to the adult stem cell niche, is a component of the tumor microenvironment (TME) that regulates stem cell activities through interactions between cells and secreted molecules (6). The TME consists of a variety of components, such as cytokine networks, immune cells, perivascular cells, fibroblasts, extracellular matrix (ECM) components, and endothelial cells (7). Tumor-associated macrophages (TAMs) are the most prevalent immune cells in the TME and can be recruited by CSCs to participate in TME formation, which can aid in CSC survival. M2 macrophages,

which are alternatively activated macrophages, have a significant influence on cancer development and progression (8), unlike M1 macrophages, which are responsible for the immune response against infections and inflammation (8).

Exosomes are small extracellular vesicles that range from 40 to 160 nm in diameter and originate from endosomes (9). It has been shown that nearly all cells secrete exosomes, which can be found in various biofluids and cell culture media (10). Exosomes represent a novel mechanism for intercellular communication between donor and recipient cells, and individuals with cancer have been found to possess increased quantities of exosomes compared with healthy individuals, highlighting the potential role of exosome-mediated cellular and communication in cancer. This communication promotes tumor formation, angiogenesis, metastasis, progression, immune evasion, and drug resistance (11). Due to their favorable biocompatibility properties and capacity for customization to target specific cells, exosomes hold promise as carriers for therapeutic payloads like microRNAs (miRNAs/miRNAs), small interfering RNA (siRNAs), and small-molecule drugs. This potential creates possibilities for transforming conventional cancer treatment approaches (12). Nevertheless, the quest for suitable exosomal molecules and donor cells to establish an effective exosomal drug delivery system remains a substantial challenge.

Extensive research has been performed to understand the complex system of communication facilitated by exosomes within the TME (9). Within the TME, macrophages play a pivotal role in intercellular communication through the release of exosomes. Macrophages are broadly categorized into two types based on their activation status: Classically activated M1 macrophages and alternatively activated M2 macrophages, which are influenced by a range of stimuli (13). TAMs exhibit a mixed M1/M2 phenotype, and macrophage-derived exosomes may vary based on their parental cell properties. For example, exosomes derived from M2 macrophages may contain higher levels of specific miRNAs compared to those derived from M1 macrophages, thereby impacting cancer progression and drug resistance (14). Hence, understanding the specific exosomes secreted by distinct macrophage phenotypes may offer therapeutic opportunities. Macrophage-derived exosomes constitute a substantial proportion of blood-borne exosomes and these may be used as potential biomarkers for diagnosing cancer through minimally invasive liquid biopsies (15). Moreover, exosomes released by macrophages can trigger immune responses that restrain cancer progression, highlighting their possible application in anti-tumor treatments (16,17). Currently, the role of M2-derived exosomes in maintaining cancer cell stemness is an active area of investigation for developing novel therapeutic approaches to target this process and improve outcomes in cancer patients.

2. CSCs in tumor progression

CSCs are a subpopulation of tumor cells that exhibit self-renewal and differentiation abilities, similar to those of normal stem cells (5,18). CSCs are hypothesized to be responsible for initiating and maintaining tumor growth, as well as conferring resistance to chemotherapy and radiation therapy. These versatile cancer cells have the capacity to differentiate into various cell types found in tumors, which enables them to drive primary tumor growth and contribute to the development of new tumors (19). Various surface markers, such as CD34+/CD38-, are used to identify CSCs in a wide range of cancers (20). By way of their pluripotency, CSCs play a pivotal role in tumorigenesis, cellular proliferation, and metastasis. Furthermore, CSCs can self-renew, making them functionally immortal. Although only a small percentage of cancer cells exhibit stemness properties, they can differentiate into a range of cancer cell types that constitute the majority of tumor cells (18). CSCs are often more tumorigenic than non-stem cancer cells. Although chemotherapy and radiotherapy can effectively kill a significant portion of the tumor mass, CSCs are typically resistant to these treatments, making it difficult to achieve significant clinical improvement (2,4,21). CSCs also have the capacity to generate a wide range of cell types within a tumor, resulting in heterogeneous progeny (22). This diversity of phenotypes stems from the inherent plasticity of CSCs, allowing them to transition between different cell states or phenotypic states. These transitions can occur spontaneously or in response to signals from the tumor microenvironment, such as changes in oxygen levels, nutrient availability, or interactions with other cells and signaling molecules (22). The phenotypic variations exhibited by CSCs are extensive and can vary depending on the tumor type and context (22). There are several common phenotypic states observed in CSCs: i) Stem-like state: CSCs maintain stem cell-like properties, characterized by their ability to self-renew and differentiate into multiple cell lineages. These cells often show increased expression of stem cell markers and signaling pathways associated with stemness (23). ii) Differentiated state: CSCs can undergo partial or complete differentiation into various cell types present in the tumor, resembling the non-CSC population. This differentiation can lead to the formation of bulk tumor cells with limited self-renewal potential (24). iii) Hybrid state: CSCs can exhibit a hybrid phenotype that combines both stem-like and differentiated characteristics. These cells possess certain stem cell properties while also displaying markers or features associated with more differentiated cells. The hybrid state may confer increased resistance to therapies and enhanced metastatic potential (24). iv) Epithelial-to-mesenchymal transition (EMT): CSCs can undergo a process known as EMT, which is associated with increased invasiveness and metastatic potential. During EMT, CSCs lose epithelial characteristics and acquire mesenchymal traits, including enhanced motility, resistance to apoptosis, and ECM remodeling abilities (25). v) Metabolic plasticity: CSCs can adapt their metabolic profile to utilize different energy sources and survive in a range of different microenvironments. They can switch between glycolysis and oxidative phosphorylation (a process known as the Warburg effect), which provides them with a survival advantage under nutrient-deprived conditions (26). Understanding and targeting the cellular plasticity of CSCs is crucial for developing effective therapeutic strategies against cancer. The ability of CSCs to transition between different phenotypic states enables them to evade therapies, contribute to tumor heterogeneity, and drive tumor relapse and metastasis (25). Overall, the characteristics of CSCs offer a valuable avenue for comprehending cancer development and the potential treatment of various cancer types.

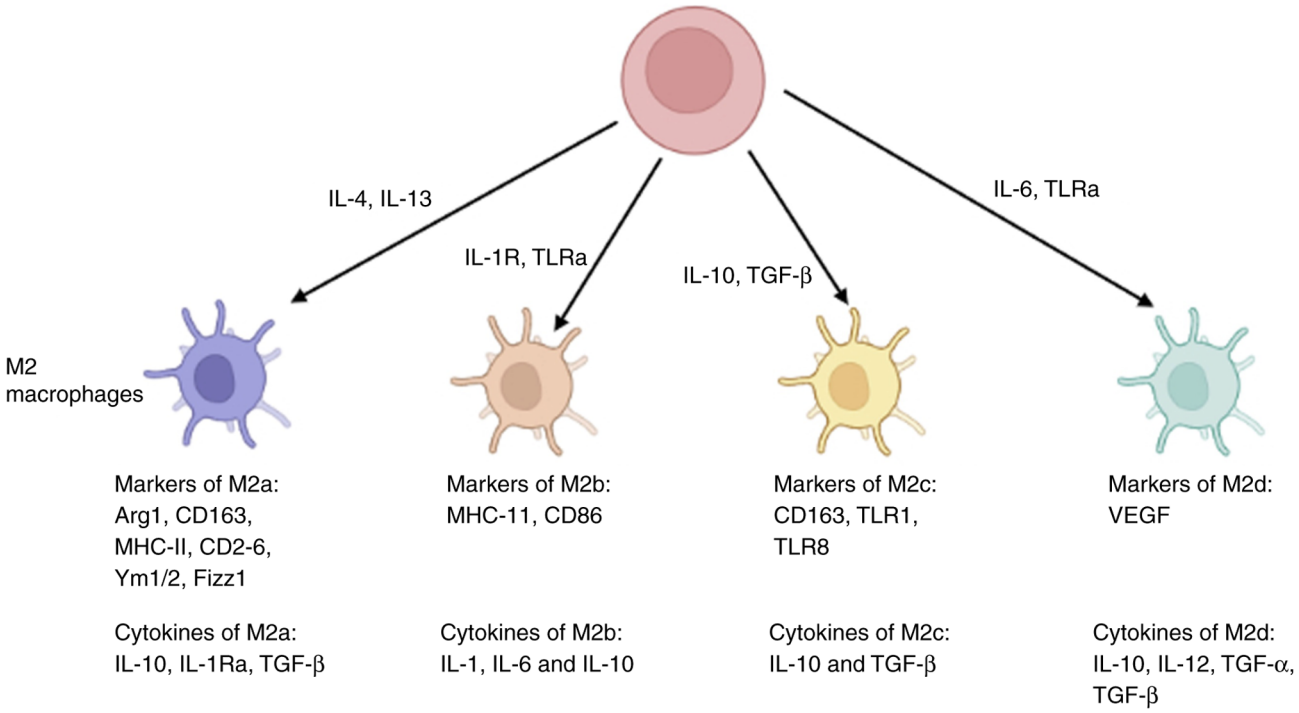

Figure 1. M2 macrophages and expression markers. Arg1, arginase 1; FIZZ1, resistin-like molecule alpha1; IL-1, interleukin-1; IL-10, interleukin-10; IL-12, interleukin-12; IL-13, interleukin-13; IL-1R, interleukin-1 receptor; IL-1Ra, interleukin-1 receptor agonists; IL-4, interleukin-4; IL-6, interleukin-6; MHC-II, major histocompatibility complex-II; TGF-β, transforming growth factor-β; TLR1, Toll-like receptor 1; TLR8, Toll-like receptor 8; TLRa, Toll-like receptor agonists; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor.

3. The role of M2 macrophages in tumor progression

Within the scientific community, an ongoing debate persists regarding the specific mechanism underlying the origin of macrophages. However, it is widely recognized that macrophages can be classified into two distinct lineages: Bone marrow-derived macrophages and tissue-resident macrophages (27,28). Tissue-resident macrophages develop during embryonic development and are self-sustaining within their specific area, while bone marrow-derived macrophages arise from monocytes differentiated by bone marrow progenitors (29). These monocytes migrate from the bloodstream to tissues during normal and inflammatory conditions and are activated by various factors. These macrophage populations have distinct distributions within the TME, with tissue-resident macrophages spreading to neighboring tumor cells early on, promoting EMT and increasing invasion (30). Furthermore, tissue-resident macrophages raise regulatory T-cell numbers to help tumor cells escape from the immune system (31). Hence, tissue-resident macrophages may present a promising target for treating tumors. There are various macrophage subtypes that can be characterized with specific markers.

Macrophages are a heterogeneous population of immune cells with a range of phenotypes and functions that actively regulate tumor progression. Among these, the M1 and M2 macrophage subtypes hold significant roles in tumor regulation. M1 macrophages exhibit a pro-inflammatory phenotype when exposed to Type 1 T helper cytokines, such as IFN-γ, and TNF-α. They secrete anti-tumor pro-inflammatory cytokines such as IL-8, TNF-α, IL-1β, and IFN-γ (32,33). Conversely, M2 macrophages are primarily activated by Type 1 T helper (Th2) cytokines, including IL-13 and IL-4, resulting in anti-inflammatory properties and tumorigenesis. M2 macrophages can be further classified into distinct subsets based on specific stimuli and markers. The M2a subset, characterized by CD206 and CD68, contributes to fibrosis, allergic responses, and parasite elimination. The M2b subset, identified by CD86 receptors, plays a vital role in immune responses (34,35). The M2c subset, distinguished by the expression of CD163 receptors, is induced by IL-10, TGF-β, or glucocorticoids and serves a critical function in anti-inflammatory processes (36,37). Finally, the M2d subset, associated with tumor progression, exhibits increased secretion of vascular endothelial growth factor (VEGF) and IL-10, along with reduced expression of TNF-α and IL-12 (38,39). Nonetheless, the precise mechanism underlying the programming of M2d macrophages remains a subject of controversy. Fig. 1 provides a depiction of the expression of markers associated with different subtypes of M2 macrophages.

Macrophages in the TME may have divergent effects on cancer progression based on their polarization status. Initially, macrophages may exhibit a pro-inflammatory response and inhibit tumor growth; however, the evidence supporting this remains limited (40). As a tumor expands, Th2 cells guide macrophages toward a pro-tumor phenotype, which promotes tumor development (41). M2 macrophages have been shown to regulate multiple aspects of tumorigenesis, such as angiogenesis, metastasis, and chemo-resistance. M2 macrophages can promote tumor cell intravasation and extravasation by secreting VEGF and epidermal growth factor (42,43). They also modulate tumor metastasis by regulating EMT and promoting ECM degradation. The majority of TME-associated macrophages

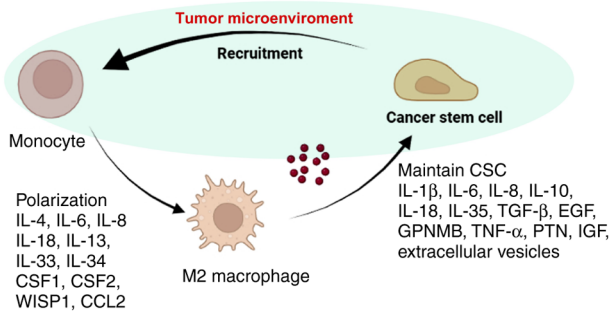

Figure 2. Interaction between M2 macrophages, CSCs and the tumor microenvironment. CCL2, C-C motif chemokine ligand 2; CSF1, colony stimulating factor 1; CSF2, colony stimulating factor 2; EGF, epidermal growth factor; GPNMB, glycoprotein non-metastatic melanoma protein B; IGF, insulin-like growth factor; IL-10, interleukin-10; IL-13, interleukin-13; IL-18, interleukin-18; IL-33, interleukin-33; IL-34, interleukin-34; IL-35, interleukin-35; IL-4, interleukin-4; IL-6, interleukin-6; IL-8, interleukin-8; PTN, pleiotrophin; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; WISP1, WNT1-inducible-signaling pathway protein 1.

tend to be M2, which creates an immunosuppressive microenvironment (44). An overview of the interactions between CSCs and M2 macrophages is shown in Fig. 2. Therefore, gaining insights into the characteristics of M2 macrophages can enhance our understanding of cancer states and enable the development of new approaches for inhibiting or eradicating cancer.

4. Characteristics and composition of macrophage-derived exosomes

The process by which exosomes are formed from macrophages follows a similar pattern to that observed in other cells. It is initiated by the inward budding of the cellular membrane, leading to the formation of endosomes (9). These endosomes then generate intraluminal vesicles (ILVs) within the cytoplasm, gradually transforming into multivesicular bodies (MVBs) (9). Throughout this process, the sorting of exosomal cargo can be influenced by various external factors. For example, in response to IL-4 stimuli, macrophage-derived exosomes selectively incorporate miRNAs (45). Moreover, macrophages activate the peroxisome proliferator-activated receptor γ pathway and transfer phosphatase and tensin homolog (PTEN) into exosomes when exposed to the microenvironment of apoptotic lung cancer cells undergoing irradiation (46). Additionally, the activation of the P2X7 signaling pathway triggered by extracellular ATP enables macrophages to transfer IL-1β and other proteins into exosomes, leading to an elevation in intracellular calcium levels (Fig. 3) (47,48).

Typically, exosomes from the inward budding of the cellular membrane can create endosomes, which develop ILVs that eventually mature into MVBs through cargo sorting and external factors. In the typical scenario, MVBs are predominantly degraded by lysosomes, and only a small fraction of them are released as exosomes through exocytosis facilitated by Rab proteins and small GTPases (49). However, when lysosomes in macrophages are defective, increased secretion of exosomes is observed (50), indicating the substantial reliance on macrophage-derived exosomes on lysosomal function. Conversely, autophagy has a diminishing effect on exosomal secretion since autophagosomes can merge with MVBs to form amphisomes, which can then be degraded by lysosomes (51). Conversely, reducing the expression of lysosome-associated membrane protein-2 and lysosome-associated membrane protein-1 hinders the fusion of amphisomes with lysosomes, resulting in an increased release of exosomes. Notably, not only endogenous factors but also exogenous stimuli, such as cellular stress impact the secretion of macrophage-derived exosomes (52). For example, macrophages release a higher number of exosomes upon stimulation by lipopolysaccharide (LPS), which upregulates the expression of Rab27b and Rab27a. However, this effect can be counteracted by IL-25 (53). In the tumor microenvironment, hypoxia can also enhance the release of macrophage-derived exosomes compared to physiological conditions (54). These exosomes become independent components of the tumor microenvironment and can affect other cells through various mechanisms. For instance, For example, LPS/IFN-γ-induced macrophage-derived exosomes can bind to extracellular endoplasmic reticulum aminopeptidase 1, which promotes macrophage phagocytosis and nitric oxide synthesis (55). Macrophage-derived exosome surface markers are specific to cell and/or tissue types and can determine the types of recipient cells (56). Different proteins, such as RAB27A and syntaxin 3, are used by macrophages from various tissues to regulate exosomal biogenesis and docking with recipient cells (57). Overall, these findings suggest that macrophage-derived exosomes play a role in cell-to-cell communication and have a wide range of effects depending on their contents and surface markers.

5. M2 macrophage-derived exosomes in cancer cell stemness

M2 macrophage-derived exosomes transfer various biomolecules, including growth factors, cytokines, miRNAs, long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs) (Table I) have been shown to promote self-renewal and survival of CSCs (58). They can also modulate the signaling pathways and molecular processes that regulate CSCs, thereby maintaining and expanding the cancer stem cell population (58).

Additionally, M2 macrophage-derived exosomes have been shown to modify the behavior of immune cells, thereby suppressing the anti-tumor immune response (59). This may further promote the survival and expansion of the cancer stem cell populations and contribute to tumor progression.

miRNA-mediated regulation of cancer cell stemness. Exosomes, which mediate cell-to-cell interactions, possess the ability to exchange genetic molecules, such as miRNAs (60). miRNAs are key to the development, polarization, and metabolic control of macrophages (61-63). To maintain a balanced mRNA environment, exosomes can rapidly eliminate excessive miRNAs in an activation-dependent manner (45). Consequently, exosomes derived from macrophages stimulated with LPS or IL-4 exhibit noticeable enrichment of specific miRNAs (64). Numerous studies have demonstrated that alterations in exosomal miRNAs derived from macrophages can significantly impact important post-transcriptional control functions in neighboring cells, including cancer cells.

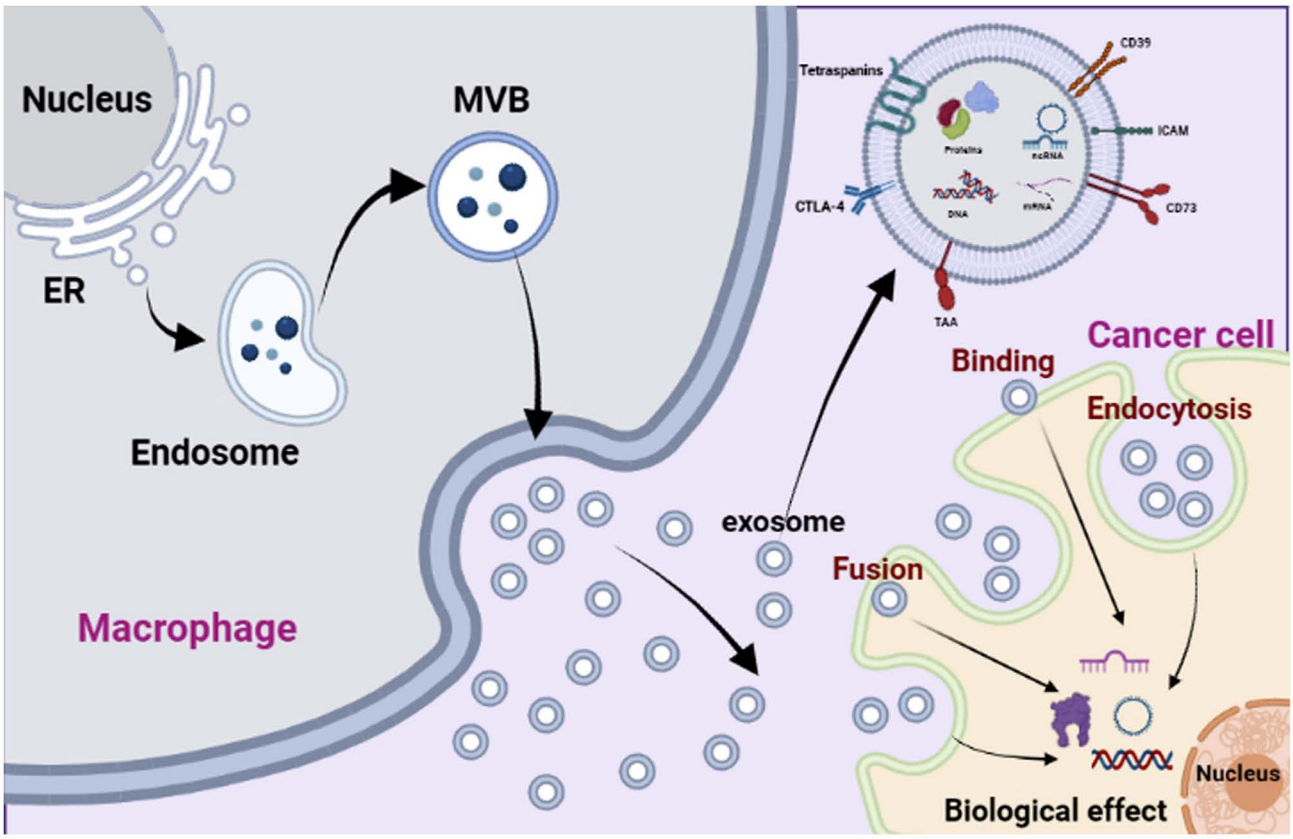

Figure 3. Interaction between M2 macrophage-derived exosomes and CSCs. CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ER, endoplasmic reticulum; ICAM, intercellular adhesion molecule; MVB, multivesicular body; TAA, tumor-associated antigens.

To date, a wide range of miRNAs sourced from exosomes of M2 macrophages have been implicated in the regulation of cancer stemness. In human colon cancer, exosomal miR-155-5p derived from M2 macrophages has been shown to augment the proliferation and anti-apoptotic capabilities of SW48 and HT29 cells. It also promotes immune escape by downregulating zinc finger CCCH-type containing 12B and upregulating IL-6, thereby increasing CD3+ T cell proliferation and the proportion of IFN-γ+ T cells (65). Another study revealed that the collaborative action of exosomal miR-155-5p and miR-21-5p from M2 macrophages promotes cell migration and invasion in colon cancer by suppressing BRG1 expression. (66); BRG1 is a crucial regulator in maintaining colorectal cancer stem cells (67). In pancreatic cancer, exosomal miR-155-5p and miR-221-5p derived from M2 macrophages were found to stimulate angiogenesis and pancreatic cancer growth by inhibiting E2F2 expression (68). E2F2 transcriptionally regulates multiple targets involved in various characteristics of CSCs, including proliferation, self-renewal, metastasis, and drug resistance (69). Furthermore, exosomal miR-193b-3p from M2 macrophages was observed to enhance the proliferation, migration, invasion, and glutamine uptake of pancreatic cancer cells by downregulating tripartite motif containing 62 (70). Similarly, exosomal miR-365 from M2 macrophages suppressed the expression of BTG2, activating the FAK/AKT pathway and promoting pancreatic cancer development (71). Inhibiting the FAK/AKT signaling pathway was found to reduce the viability of human breast cancer stem cells (72). Additionally, exosomal miR-501-3p derived from M2 macrophages was identified to hinder the tumor suppressor TGFβ receptor 3 gene, thereby facilitating the progression of pancreatic cancer through the activation of the TGF-β signaling pathway (73). It is important to note that the TGF-β signaling pathway has been demonstrated to enhance pancreatic cancer stemness (74,75). Interestingly, miR-21-5p from extracellular vesicles derived from M2 macrophages was found to promote the differentiation and activity of pancreatic cancer stem cells by suppressing Krüppel-like factor 3 (KLF3) expression (76). In lung cancer, exosomal miR-1911-5p from M2 macrophages facilitated cell migration and invasion in lung adenocarcinoma by downregulating zinc finger and BTB domain containing 4 expression, which is mediated by CUGBP Elav-like family member 2 (77). Additionally, exosomal miR-3917 from M2 macrophages promoted lung cancer progression by inhibiting G protein-coupled receptor kinase 6 (78), a factor involved in maintaining self-renewal of hematopoietic stem cells (79). Furthermore, exosomal miR-501-3p from M2 macrophages represses WD repeat domain 82, contributing to the progression of lung cancer (80). Notably, M2 macrophage-derived exosomal miR-942 suppresses forkhead box protein O1 (FOXO1) expression, promoting the progression of lung adenocarcinoma (81), FOXO1 acts as a key inhibitor of cancer cell stemness in various cancer types (82,83). In gastric cancer, exosomal miR-487a from M2 macrophages advances disease progression by suppressing TIA1 expression (84). Moreover, exosomal miR-588 from M2 macrophages contributes to cisplatin resistance in gastric cancer cells by partially inhibiting cylindromatosis expression (85), which regulates the

Table I. Role of M2 macrophage-derived exosomal non-coding RNAs in regulating cancer progression.

Types of non-coding RNAs	Name of non-coding RNAs	Related target/ signaling pathway	Cancer type	(Refs.)
miRNA	miR-155-5p	ZC3H12B	Colon cancer	(65)
	miR-155-5p	BRG1	Colon cancer	(66)
	miR-186-5p	DLC1	Colon cancer	(152)
	miR-21-5p	BRG1	Colon cancer	(152)
	miR-221-3p	CDKN1B	Epithelial ovarian cancer	(89)
	miR-487a	TIA1	Gastric cancer	(84)
	miR-588	CYLD	Gastric cancer	(85)
	miR-27b-3p	MLL4/PRDM1	Glioblastoma	(87)
	miR-15a	PI3K/AKT/mTOR signaling	Glioma	(93)
	miR-92a	PI3K/AKT/mTOR signaling	Glioma	(93)
	miR-660-5p	KLF3	Hepatocellular carcinoma	(88)
	miR-222-3p	PDLIM2/PFKL	Laryngeal squamous cell carcinoma	(153)
	miR-1911-5p	CELF2/ZBTB4 signaling	Lung cancer	(77)
	miR-942	FOXO1	Lung cancer	(81)
	miR-3917	GRK6	Lung cancer	(78)
	miR-501-3p	WD repeat domain 82	Lung cancer	(80)
	miR-155-3p	WD repeat domain 82	Medulloblastoma	(154)
	miR-31-5p	LATS2/Hippo signaling	Oral squamous cell carcinoma	(91)
	miR-221-3p	SOCS3/JAK2/STAT3	Osteosarcoma	(90)
	miR-193b-3p	TRIM62	Pancreatic cancer	(70)
	miR-21-5p	KLF3	Pancreatic cancer	(76)
	miR-155-5p	E2F2	Pancreatic cancer	(68)
	miR-221-5p	E2F2	Pancreatic cancer	(68)
	miR-365	BTG2/FAK/AKT	Pancreatic cancer	(71)
	miR-501-3p	TGFBR3-mediated TGF-β signaling	Pancreatic cancer	(73)
	miR-21-5p	PTEN/Akt signaling	Renal cell carcinoma	(155)
lncRNA	lncMMPA	Glycolysis pathway	Hepatocellular carcinoma	(106)
	H19	ULK1	Bladder cancer	(108)
	lncRNA CRNDE	PTEN	Gastric cancer	(115)
	AGAP2-AS1	miR-296/Notch2signaling	Lung cancer	(112)
	AFAP1-AS1	miR-26a/ATF2 signaling	Esophageal cancer	(113)
circRNA	Circ_0008253	Not examined	Gastric cancer	(121)
	Circ_0020256	miR-432-5p/ E2F3 signaling	Cholangiocarcinoma	(122)
	Circ_0001610	miR-139-5p/cyclin B1 signaling	Endometrial cancer	(123)
	Circ_TNFRSF21	mMiR-3619-5p/ ROCK signaling	Cutaneous squamous cell carcinoma	(124)

lncRNA, long non-coding RNA; ATF2, activating transcription factor 2; BRG1, BRM/SWI2-related gene 1; CDKN1B, cyclin-dependent kinase inhibitor 1B; CELF2/ZBTB4, CUGBP Elav-like family member 2/zinc finger and BTB domain containing 4; CYLD, cylindromatosis; DCL1, deleted in liver cancer 1; FOXO1, forkhead box O1; KLF3, Krüppel-like factor 3; LATS2, large tumor suppressor kinase 2; MLL4/PRDM1, mixed-lineage leukemia 4/positive regulatory domain I; PDLIM2/PFKL, PDZ and LIM domain 2/phosphofructo-1-kinase isozyme B; PTEN, phosphatase and tensin homolog; SOCS3, suppressor of cytokine signaling 3; TGFBR3, transforming growth factor beta receptor 3; TRIM62, tripartite motif containing 62; ULK1, Unc-51 like autophagy activating kinase 1; ZC3H12B, zinc finger CCCH-type containing 12B.

proliferation of esophageal cancer stem-like cells through the cylindromatosis pathway (86).

In glioblastoma, M2 macrophage-derived exosomal miR-27b-3p represses mixed-lineage leukemia 4/positive regulatory domain 1 signaling, resulting in the activation of IL-33 and maintenance of stem-like properties in glioblastoma stem cells (87). Studies on hepatocellular carcinoma indicated that exosomal miR-27b-3p from M2 macrophages enhanced tumor development by suppressing KLF3 (88), whereas inhibition of KLF3 was found to stimulate the differentiation and activity of pancreatic cancer stem cells (76). In epithelial ovarian cancer, exosomal miR-221-3p from M2 macrophages promotes disease progression by suppressing cyclin-dependent kinase inhibitor 1B. Similarly, exosomal miR-221-3p derived from M2 macrophages enhance the growth and metastasis of osteosarcoma by repressing suppressor of cytokine signaling 3, activating JAK2/STAT3 signaling (89), which plays a critical role in maintaining cancer cell stemness (90). In oral squamous cell carcinoma, exosomal miR-31-5p from M2 macrophages hinders the tumor suppressor large tumor suppressor kinase 2 gene, facilitating cancer progression by inhibiting the Hippo signaling pathway (91), which promotes the transition EMT and the maintenance of cancer stem cells (92). Conversely, in glioma, M2 macrophage-derived exosomal miR-15a and miR-92a suppress cyclin D1 and RAP1B, respectively, resulting in the inhibition of cell migration and invasion via the PI3K/AKT/mTOR pathway (93). The PI3K/AKT/mTOR signaling pathway has been shown to regulate cancer stemness (94). Notably, exosomal miR-223 derived from macrophages exhibits divergent effects in different cancer types, despite its involvement in regulating the biological function of cancer stem cells. The expression levels of miR-223 vary across different cancer types, with increased expression in metastatic gastric and ovarian cancers, but decreased expression in hepatocellular and esophageal cancer (95,96). This indicates a contradictory role for miR-223 in cancer. Furthermore, exosomal miR-223 from macrophages can promote drug resistance in epithelial ovarian carcinoma cells by inhibiting PTEN expression (97), while in breast cancer cells, it can induce invasion and metastasis by suppressing Mef2c expression (98). However, conflicting findings suggest that exosomal miR-223 from macrophages inhibits cancer cell proliferation in hepatocellular cancer cells by downregulating stathmin 1 and insulin-like growth factor 1 receptor expression (99). It is possible that miR-223 induces macrophages to adopt either an anti-tumor or pro-tumor phenotype in different pathological conditions, leading to pleiotropic effects in cancer cells, exhibiting both suppressive and promotive roles.

lncRNA-mediated regulation of cancer cell stemness. lncRNAs are RNA molecules that are >200 nucleotides in length and lack protein-coding capacity. Despite their non-coding nature, they play crucial roles in various cellular processes, including regulation of gene expression, epigenetic modifications, chromatin remodeling, and mRNA processing. In recent years, extensive research has highlighted the significance of lncRNAs in cancer development and progression (100,101). Dysregulation of lncRNAs can disrupt normal cellular processes, leading to uncontrolled cell growth, survival, and metastasis, which are all characteristic features of cancer. Previous research has primarily focused on studying the functions and mechanisms of lncRNAs within individual cells, but there has been limited investigation into the role of lncRNAs carried by exosomes secreted by macrophages in facilitating communication between cells. However, recent studies have shown that exosomes released by macrophages can deliver a specific lncRNA called HIF-1α-stabilizing lncRNA to breast cancer cells. This delivery process then influences the glycolysis of cancer cells by interacting with a protein called prolyl hydroxylase domain 2, leading to the stabilization of HIF-1α (102). HIF-1α is known to play a role in the development of cancer stemness under conditions of hypoxia (103). These findings suggest that exosomal lncRNAs derived from macrophages have a positive impact on cancer stemness. Additionally, Yin *et al* (104) discovered that exosomal lncRNA SET-binding factor 2 antisense RNA 1 derived from M2 macrophages can be transferred to pancreatic cancer cells, promoting cancer progression by suppressing miR-122-5p and increasing the expression of a protein called X-linked inhibitor of apoptosis protein. Notably, miR-122-5p has been associated with cervical cancer stem cell self-renewal and differentiation (105). In hepatocellular carcinoma, exosomes derived from M2 macrophages play a role in promoting malignancy by transferring lncMMPA to tumor cells. This transfer inhibits miR-548 and leads to the upregulation of aldehyde dehydrogenase 1 family member A3 (ALDH1A3) expression (106), whereas inhibition of ALDH1A3 can impede cancer cell stemness (107). In bladder cancer, M2 macrophage-derived lncRNA H19 promotes autophagy in bladder cells by stabilizing Unc-51-like kinase 1 (108). Notably, lncRNA H19 has been extensively studied for its involvement in promoting cancer stemness across various cancer types (109-111). In lung cancer, exosomal lncRNA AGAP2 antisense RNA 1 derived from M2 macrophages enhances radiotherapy immunity by reducing miRNA-296 and increasing NOTCH2 expression. Activation of the Notch2 signaling pathway has been associated with promoting lung cancer stemness (112). In esophageal cancer, exosomal lncRNA AFAP1 antisense RNA 1 from M2 macrophages affects cell migration and metastasis by repressing miR-26a expression, thereby promoting activating transcription factor 2 activity (113). It is worth noting that miR-26a can regulate the activating enhancer binding Protein 2 α/Nanog signaling axis related to glioma cancer stemness (114). In gastric cancer, M2 macrophage-derived lncRNA colorectal neoplasia differentially expressed (CRNDE) contributes to cisplatin resistance (115). Furthermore, lncRNA CRNDE has been implicated in the regulation of biological characteristics of glioma stem cells (116). In summary, these findings shed light on the role of exosomal lncRNAs in mediating interactions between cells within TME.

circRNA-mediated regulation of cancer cell stemness. CircRNAs are a type of non-coding RNA characterized by a closed-loop structure and play crucial roles in gene regulation, development, and disease progression. Emerging studies suggest that circRNAs may participate in modulating CSCs across various cancer types (117,118). Specifically, certain circRNAs have been shown to influence the differentiation and self-renewal of CSCs in breast, glioblastoma, and colorectal cancer (119). Additionally, certain circRNAs have been found

to modulate the expression of genes that are important for CSC maintenance and survival (120). One mechanism through which circRNAs exert their influence on CSCs is by interacting with miRNAs. By acting as miRNA sponges, circRNAs can bind to and sequester miRNAs, thereby regulating the expression of miRNA target genes crucial for CSC function. For example, Yu *et al* (121), revealed that macrophage-derived exosomes regulate gastric cancer cell resistance to oxaliplatin by encapsulating circ_0008253. However, the role of circ_0008253 in CSCs has not yet been investigated. Another study by Chen *et al* (122) revealed that M2 macrophage-derived exosomal circ_0020256 enhances cholangiocarcinoma progression by targeting miR-432-5p/E2F3 axis. Gu *et al* (123) identified that M2 macrophage-derived exosomal circ_0001610 reduces endometrial cancer radiosensitivity. Moreover, M2 macrophage-derived exosomal circ_TNFRSF21 facilitates angiogenesis in cutaneous squamous cell carcinoma through the regulation of miR-3619-5p/Rho-associated coiled-coil containing protein serine/threonine kinase signaling (124). Nevertheless, the specific roles of these circRNAs in CSCs remain to be investigated.

M2 macrophage-derived exosomal proteins in cancer stemness. Proteomics has been widely employed to analyze protein expression profiles (125). By utilizing proteomics, it was uncovered that treating macrophages with LPS/IFN-γ led to the upregulation of 24 proteins and the downregulation of eight proteins in macrophage-derived exosomes (55). Additionally, proteomic analysis of the culture media from the co-culture of colorectal cancer and Ana-1 cells identified an enrichment of proteins related to RNA processing, including several subunits of the 20S proteasome and ribosomal proteins, in M2 macrophage-derived exosomes (126). These findings suggest that proteins present in M2 macrophage-derived exosomes may contribute to tumor survival by degrading misfolded or denatured proteins in cancer cells. Nevertheless, to obtain a more accurate representation of the *in vivo* environment, it is crucial to isolate solid tumor tissue-derived exosomes, which requires suitable models and an adequate number of samples. Due to the sensitivity of macrophages and their exosomes to the surrounding conditions, the contents of macrophage-derived exosomes and macrophage phenotypes can vary under different conditions or in different types of cancer. The activities of proteins originating from macrophage-derived exosomes are primarily determined by the specific recipient cells they interact with. In the context of high-grade serous ovarian carcinoma, the inclusion of GATA binding protein 3 within macrophage-derived exosomes has been observed to facilitate the advancement of tumors (127). In gastric cancer, macrophages are the primary source of apolipoprotein E (ApoE), which is also abundant in their exosomes. When cancer cells internalize ApoE-containing exosomes derived from macrophages, they activate the PI3K/AKT signaling pathway, thereby promoting cancer cell migration (128).

Furthermore, macrophage-derived exosomes can influence the adaptability of cancer cells and contribute to metastasis. Kim *et al* (46) demonstrated that macrophages can deliver an increased amount of PTEN protein to recipient cells via exosomes when exposed to irradiated apoptotic lung cancer cells, thereby impeding EMT. Conversely, exosomal ADAM domain 15, a protein secreted by M2 macrophages, inhibits cancer cell migration and growth (129). In addition to macromolecular proteins, cytokines also play a critical role in cancer and can be found in M2 macrophage-derived exosomes. For instance, mouse macrophages release various cytokines in exosomes upon LPS stimulation (64). In one study, M2 macrophages cultured with apoptotic breast cancer cells after chemotherapy increased the production of IL-6 in their exosomes, which were then transferred to cancer cells (130). This process promoted cancer cell metastasis and proliferation by enhancing STAT phosphorylation. While cytokines have been extensively investigated in the context of non-exosomal secretion pathways, exploring whether these cytokines exhibit enhanced efficacy through exosomal pathways would be valuable.

Other macrophage-derived exosomal cargos in cancer stemness. Several studies have provided compelling evidence that macrophage-derived exosomes contain a diverse array of components, including miRNAs, lncRNAs, proteins, mRNA, tRNA and ribosomes (131). Recent research has highlighted the significant role of exosomal mitochondrial/nuclear DNA derived from cancer cells in tumor immunity (132). However, the presence of functional endogenous DNA in macrophage-derived exosomes remains uncertain. Nonetheless, artificial dsDNA has been detected in macrophage-derived exosomes in pancreatic cancer (14). Importantly, M2 macrophage-derived exosomes enriched with arginase-1 can stimulate the migration and proliferation of glioblastoma cells (133). Moreover, once macrophage-derived exosomes are released into the extracellular microenvironment, they may serve as primitive particles within the ECM (9). This is supported by the observation that components in macrophage-derived exosomes are capable of synthesizing thromboxane B2, thromboxane, and specific proteins (126). Further investigation is warranted to explore the potential independent functions of macrophage-derived exosomes separate from their parent cells.

6. Therapeutic agents targeting M2 macrophages for cancer treatment in clinical trials

Both preclinical and clinical investigations have underscored the therapeutic potential of targeting two signaling pathways, namely the C-C chemokine receptor type 2 (CCR2)-C-C Motif chemokine ligand 2 (CCL2) axis and the C-C Motif chemokine ligand 12 (CXCL12)-C-X-C Motif chemokine receptor 4 (CXCR4) pathway, to hinder the recruitment and infiltration of TAMs into the TME. These approaches hold promise for patients with solid tumors (134). For example, an anti-CCL2 antibody (carlumab) inhibited macrophage infiltration in mice and is presently being tested in clinical trials (NCT 00992186) for the treatment of solid tumors and metastatic castrate-resistant prostate cancer (135). However, carlumab alone only produces a temporary reduction in serum CCL2 levels without significant antitumor effects. Nevertheless, when combined with conventional chemotherapeutic regimens such as paclitaxel and carboplatin, it enhances the antitumor response. Similarly, clinical trials have revealed that inhibiting the CXCL12-CXCR4 signaling pathway can result in TAM exclusion and effective treatment of solid tumors (136).

For example, a CXCR4 antagonist called (Plerixafor) impedes tumor angiogenesis by inhibiting the release of VEGF-A from TAMs and has been employed in the treatment of solid tumors and pediatric cancers (137-139). LY2510924, a CXCR4 antagonist, has also undergone clinical trials (NCT02737072) for the treatment of solid tumors (134).

TAM recruitment and polarization are heavily influenced by colony-stimulating factor-1 receptor (CSF-1R)/colony-stimulating factor-1 (CSF-1) pathway, thus, there have been endeavors to block this signal in TAMs for the treatment of solid tumors (140). Clinical trials have been conducted with Emactuzumab (RG7155) (NCT01494688). This treatment has demonstrated a reduction in CD163+/CSF-1R+ macrophages in diffuse-type giant cell tumors and an increase in CD8+/CD4+ ratio (134). Clinical trials are also underway to explore the combination of Emactuzumab with chemotherapy (NCT02760797) and immunotherapy (NCT02323191) for solid tumor treatment. Clinical trials have utilized CSF-1R-specific inhibitors for the treatment of solid tumors. Both CSF-1R inhibitors and antibodies have exhibited therapeutic improvements in clinical trials. An example of this is the utilization of the CSF-1R inhibitor BLZ945, either alone or in conjunction with anti-programmed cell death protein 1 (PD1) antibody immunotherapy (NCT02829723), which has demonstrated the ability to impede macrophage recruitment and promote a change in macrophage polarization towards phenotypes that are beneficial in combating tumors (134). The efficacy of this combination is presently being assessed in clinical trials as a potential treatment for advanced-stage solid tumors.

Although strategies that aim to eliminate or hinder the recruitment of TAMs can delay tumor progression, they often have systemic toxicities as they target all macrophages and can be quickly compensated by TAMs. Moreover, discontinuation of CCR2/CCL2 inhibitors can lead to accelerated metastasis in breast cancer due to the sudden release of monocytes that were previously trapped in the bone marrow (141). To overcome these limitations, alternative approaches have garnered interest, such as re-educating macrophages to adopt an anti-tumor phenotype. One such approach involves using inhibitors that block receptor signals on macrophages responsible for modulating phagocytosis. Tumor cells frequently overexpress a signaling molecule called CD47, which acts as a 'do not eat me' signal and suppresses macrophage phagocytic capacity by interacting with signal regulatory protein α (SIRPα). Anti-CD47 antibodies can disrupt the CD47-SIRPα axis, restoring the ability of macrophages to engulf tumors (126). Several conventional anti-CD47 antibodies have shown success in preclinical and clinical trials. For example, the anti-CD47 antibody Hu5F9-G4 inhibits the interaction between CD47 and SIRPα, promoting macrophage-mediated phagocytosis and the elimination of cancer cells; this antibody has been tested in clinical trials (NCT02953509 and NCT02216409) for the treatment of solid tumors and various hematological malignancies (142). Additionally, polypeptides or recombinant proteins derived from SIRPα, such as engineered high-affinity SIRPα proteins, can act as decoys by binding to CD47 and disrupting CD47-SIRPα signaling. Studies have demonstrated that the recombinant protein TTI-621, consisting of the N-terminal domain of SIRPα fused to human IgG1, suppresses tumor growth by enhancing macrophage-mediated phagocytosis of solid tumor cells (143). Currently, TTI-621 is undergoing clinical investigation for the treatment of solid tumors (NCT02663518 and NCT02890368). However, CD47 is expressed on both healthy and tumor cells. Therefore, targeting CD47 will inevitably lead to the elimination of healthy cells that express CD47, including red blood cells and thrombocytes. The unintended consequences of this approach, such as thrombocythemia and anemia, result in a reduced maximum tolerated dose during clinical trials. Consequently, these off-target effects limit the impact on the tumor (144).

CD40, a member of the TNF receptor superfamily, is expressed on various antigen-presenting cells and certain tumor cells. Activation of TAMs by agonistic anti-CD40 antibodies has been shown to stimulate the secretion of pro-inflammatory cytokines such as nitric oxide and TNF-α, activating effector T cells and restoring tumor immune surveillance. Selicrelumab in combination with immunotherapy, such as atezolizumab, has been tested in clinical trials (NCT02304393) for the treatment of solid tumors and has been demonstrated to significantly enhance macrophage phagocytic activity (134).

Toll-like receptor (TLR) activation is essential for stimulating the innate immune response of macrophages, driving them toward the M1 phenotype associated with anti-tumor activity. The activation of multiple TLR signals enhances macrophage phagocytic activity and promotes anti-tumor responses. For example, TLR4 and TLR5 agonists have been observed to polarize a greater number of CD206+ M2 TAMs towards the CD86+ M1 phenotype, effectively suppressing tumor growth without significant toxicity (145). Clinical trials have evaluated the TLR9 agonist, IMO-2125, for the treatment of refractory solid tumors and metastatic melanoma (NCT04126876 and NCT03052205), resulting in macrophage polarization towards an anti-tumor phenotype and subsequent tumor regression (134). However, TLR agonists can upregulate the expression of programmed death-ligand 1 (PD-L1) in macrophages, limiting the anti-tumor response. To overcome this limitation, the combination of IMO-2125 with immunotherapy, such as ipilimumab, has been explored to enhance the effectiveness of cancer treatment. Additionally, SD101, another TLR9 agonist, is currently undergoing clinical trials (NCT03007732) in combination with PD-1 blockade to augment therapeutic efficacy (134). Table II provides a summary of ongoing clinical trials investigating therapeutic agents targeting M2 macrophages for cancer treatment.

7. Possible therapeutic approaches involving exosomes derived from macrophages in cancer treatment

The utilization of macrophage-derived exosomes in cancer therapy is potentially significant. These exosomes have the ability to deliver targeted drugs and nanomaterials to specific recipient cells through cargo transfer. They exhibit biocompatibility and can facilitate drug transport across natural barriers, including the blood-brain barrier, enabling the delivery of brain-derived neurotrophic factors for the treatment of central nervous system diseases and brain tumor therapy while minimizing toxicity (146). Furthermore, macrophage-derived exosomes have the potential to mitigate adverse reactions in drug therapy. Studies have demonstrated that cisplatin-loaded exosomes derived from M1 macrophages

Table II. Therapeutic agents targeting M2 macrophages for cancer treatment in clinical trials.

Type of compound	Compounds	Tumor type	Clinical trial	Clinical phase
CCL2 inhibitor	Carlumab	Solid tumors	NCT01204996	I
CD40 agonist	Selicrelumab	Solid tumors	NCT02304393	I
	SEA-CD40	Solid tumors	NCT02376699	I
CD47-SIRPa inhibitor	Hu5F9-G4	Advanced solid malignancies	NCT02216409	I
CSF-1R antagonists	SNFX-6352	Advanced solid tumors	NCT03238027	I
CSF-1R antibody	Emactuzumab	Advanced solid tumors	NCT01494688	I
	FPA008	Advanced solid tumors	NCT02526017	I
CSF-1R inhibitor	PLX3397	Advanced solid tumors	NCT01596751	II
	ARRY-382	Advanced solid tumors	NCT02880371	II
	Pexidartinib	Advanced solid tumors	NCT02734433	I
	BLZ945	Advanced solid tumors	NCT02829723	I
	JNJ-40346527	Prostate cancer	NCT03177460	I
	IMC-CS4	Advanced solid tumors	NCT01346358	I
	PXL7486	Advanced solid tumors	NCT01804530	I
	AMG 820	Solid tumors	NCT01444404	I
CXCR4 antagonist	Plerixafor	Solid tumors	NCT01225419	II
CXCR4 antagonist peptide	LY2510924	Solid tumors	NCT02737072	I
IL-1R antagonist	Anakinra	Advanced solid tumors	NCT01624766	I
PI3Kg inhibitor	IPI-549	Advanced solid tumors	NCT02637531	Ib
SIRPa-IgG1 Fc	TTI-621	Solid tumors	NCT02663518	I
TLR4 agonist	GSK1795091	Advanced solid tumors	NCT03447314	I
TLR7/8 agonist	Telratolimod (MEDI9197)	Solid tumors	NCT02556463	I
TLR9 agonist	IMO-2125	Refractory solid tumors, metastatic melanoma	NCT03052205	I
	SD101	Solid tumors	NCT03007732	II
Vasculature-modulating agent Ang2/VEGF	Vanucizumab	Advanced/metastatic solid tumors	NCT02665416	I
Vitamin-D-binding protein, macrophage-activating factor	EF-022 (Efranat)	Solid tumors	NCT02052492	I

Ang2, angiopoietin-2; CCL12, C-C motif chemokine ligand 2; CSF-1R, colony stimulating factor 1 receptor; CXCR4, C-X-C motif chemokine receptor 4; IL-1R, interleukin-1 receptor; SIRPa, signal regulatory protein alpha; TLR4, Toll Like receptor 4; TLR7/8, Toll like receptor 7/8; TLR9, Toll like receptor 9; VEGF, vascular endothelial growth factor.

enhance the anti-cancer effects of a drug by suppressing cancer cell proliferation, inducing apoptosis, and improving drug sensitivity (147). Additionally, macrophages, particularly M1 macrophages, can transport paclitaxel and overcome drug resistance mechanisms, resulting in potent anti-tumor effects (148).

Exploring the biogenesis and composition of macrophage-derived exosomes holds promise for advancing anti-tumor therapies. Inhibiting exosome formation and secretion may offer the potential for anti-tumor treatment. Exosomes released by macrophages can induce cancer cells to express PD-L1 proteins, which play a crucial role in tumor immune escape. However, the use of GW4869, an inhibitor of exosomal secretion, can counteract this induction (149,150). Inhibiting exosome biogenesis *in vivo* may have implications for normal cellular functions, potentially leading to adverse effects on other intracellular transport processes. Therefore, it is crucial to exercise caution and conduct thorough investigations when developing cancer therapeutic strategies targeting exosome biogenesis. In terms of composition, ovatodiolide, a macrocyclic bioactive compound, has demonstrated its ability to reduce the abundance of M2 macrophage-derived exosomal miR-21, consequently suppressing bladder carcinogenesis (151). This discovery suggests that macrophage-derived exosomal miRNAs hold promising clinical potential for cancer treatment. In conclusion, the development of therapeutic approaches

for the complex roles of macrophage-derived exosomes should prioritize optimizing treatment efficacy while minimizing adverse reactions during the design of clinical trials.

8. Conclusions and future perspectives

M2 macrophages and the exosomes they release play a vital role in supporting CSCs and facilitating cancer progression. Through secretion of growth factors, cytokines, and immunosuppressive substances, M2 macrophages contribute to tumor growth and progression. These M2-derived exosomes further promote tumor development by transferring genetic material and influencing the immune response against cancer. The exploration of M2 cell-derived exosomes holds significant implications for the development of novel approaches in cancer treatment. Two potential avenues for therapeutic intervention involve targeting M2 macrophages and their exosomes, as well as utilizing exosome-based therapies. By directing efforts towards M2 macrophages and their exosomes, it becomes possible to limit their support to the tumor and stimulate an immune response against cancer. Additionally, exosomes can serve as a therapeutic tool by delivering therapeutic agents to cancer cells and modulating the immune response. Further research is required to fully comprehend the role of M2-derived exosomes in cancer and to develop effective therapeutic strategies. Specifically, there is a need to obtain deeper insights into the mechanisms by which M2-derived exosomes contribute to the maintenance of cancer stem cells and to develop targeted therapeutic strategies focusing on M2-derived exosomes in cancer due to their critical involvement in disease progression. In conclusion, studying M2 cell-derived exosomes in cancer has the potential to offer a better understanding of the mechanisms driving cancer progression and to guide the development of innovative therapeutic approaches. However, extensive research is essential to gain a comprehensive understanding of the role of M2 cell-derived exosomes in cancer.

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Availability of data and materials

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Authors' contributions

YL, WZ and RZ were involved in the conceptualization of the study. XL, LY, CC, JL and XY were involved in the preparation of the figures and tables, and edited the manuscript. WZ, JL and RZ were involved in the curation of the data for inclusion in the review. WZ and YL were involved in the writing and preparation of the original draft of the manuscript. YL was involved in funding acquisition. All authors have read and agreed to the published version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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