Review

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Therapeutic potentials of mesenchymal stem cell-derived exosomes for major solid malignancies: A narrative systematic review

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SUMMARY: Treatments for solid tumors, the most common malignant neoplasms, are often confounded by tumor microenvironments that impede the achievement of uniform anti-tumor effects throughout the entire malignant mass, which contributes to recurrence and progression, negatively impacting clinical outcomes. Improved treatment methods for solid malignancies are therefore needed. Mesenchymal stromal cells (MSCs) have been investigated for treatments for various types of solid tumor cancers due to their ability to target tumor cells with similar cell surface protein profiles. MSC-derived exosomes (MSC-Exos) elicit many of the tumor cell responses produced by MSC with no potential for differentiation and reduced risks of adverse effects. We surveyed the literature and clinical trials registries to identify studies investigating MSC-Exo-based anti-cancer therapies for gastric cancer, colorectal cancer, breast cancer, lung cancer, brain cancer, pancreatic cancer, and urological malignancies, and summarize the results of relevant studies herein to provide a comprehensive description of the therapeutic effects and potential clinical applications of MSC-Exos for the treatment of solid tumor malignancies. We include a summary of relevant clinical trials performed to date in an attempt to assess the data available regarding MSC-Exo safety, and propose future efforts regarding the requirements for transitioning forward from phase-1, 2 trials.

Keywords: exosome, solid malignant tumor, mesenchymal stem cell, extracellular vesicle, epithelial-to-mesenchymal transition

1. Introduction

Solid malignant tumors, the most common malignant neoplasms, account for about 80% of the most prevalent human cancers (*1*). The treatment of solid tumors often involves multiple therapeutic strategies, including surgery, chemotherapy, radiation, targeted therapy, and immune therapy. The effectiveness of such treatments depends on a number of factors associated with the tumor microenvironment (TM) that impede the achievement of uniform anti-tumor effects throughout the entire malignant mass (*2*). The resulting therapeutic inadequacies can contribute to the persistence of residual tumor cells, leading to recurrence and progression, which negatively impact clinical outcomes (*3,4*).

The physical structure of solid tumors contributes to the reduced effectiveness of chemotherapy, internal radiotherapy, targeted therapy, and immunotherapies (*5*). The dense tissue and abnormal vascularization of solid tumors can affect the penetration and distribution of therapeutic molecules within the malignant cell mass (*2,6*). Consequently, the high dosages required to overcome these structural obstacles often result in toxicity due to the limited specificity and moderate rates of off-target effects of chemotherapy drugs (*7,8*). Primary and secondary resistance to immunotherapies and tumor-targeted therapies also occurs due to both genetic and non-genetic mechanisms that often contribute to tumor cell plasticity (*9,10*). Heterogeneity in the TM can also result in the formation of hypoxic regions that locally inhibit free radical formation, which plays critical roles in the mechanisms of action of radiotherapy, immunotherapy, and many chemotherapy drugs (*5,11-13*). Improving the effectiveness of solid tumor treatments will likely require overcoming these challenges to varying extents.

Mesenchymal stromal cells (MSCs) are multipotent stem cells capable of self-renewal and cell differentiation (*14*). MSC-based cancer therapies seek to utilize the tumor-homing properties of MSCs and their selective inhibition of tumor growth and progression (*15-17*). However, MSC can contribute to tumor progression under certain circumstances (*18-20*). MSC-derived exosomes (MSC-Exos) have been shown to elicit many of the tumor cell responses produced by MSC (*21-23*) with no potential for differentiation and reduced risks of adverse effects (*21,24*), suggesting that the use of MSC-Exo-based biologicals might represent an important new adjuvant to current treatment strategies (*21,25-27*). This review summarizes the current body of research toward the application of MSC-Exos for the anti-cancer treatments, and discusses the efficacy and safety of MSC-Exo-based treatments for solid tumor cancers.

2. Literature search

The primary goal of our review was to summarize studies investigating the use of MSC-Exos for anti-tumor treatments of the following solid tumor malignancies: gastric cancer, colorectal cancer, breast cancer, lung cancer, brain cancer, pancreatic cancer, or urological cancer. We searched the PubMed database for literature published in English between January 1, 2005 and March 1, 2025 (the approximate date of the final revisions of this manuscript) to identify studies investigating the use of MSC-Exos for anti-cancer therapies using the following search criteria: (mesenchymal stem cells [Title/Abstract]) AND ((extracellular vesicles [Title/Abstract]) OR (exosomes [Title/Abstract])) AND ((solid cancer [Title/Abstract]) OR (gastric cancer [Title/Abstract]) OR (colorectal cancer [Title/Abstract]) OR (breast cancer [Title/Abstract]) OR (lung cancer [Title/Abstract]) OR (brain cancer [Title/Abstract]) OR (pancreatic cancer [Title/Abstract]) OR (urological cancer [Title/Abstract])). The search retrieved 148 results. Endnote software (Clarivate; Philadelphia, USA) was used to search for duplicate publications, and no duplicates were identified. The title, abstract, and full-text articles were subjected to manual examination. Articles meeting any of the following criteria were excluded: (1) investigations of extracellular vesicles other than exosomes, (2) investigations involving exosomes not derived from mammalian MSC, (3) studies examining exosomes derived from tumor cells, and (4) studies using exosomes to develop diagnostic or prognostic biomarkers. We excluded 62 articles. We searched the references of the included review articles to identify additional relevant publications, which resulted in the selection of an additional 22 articles for screening, of which 20 were excluded, leaving a total of 88 articles included.

We performed a search of the US National Library of Medicine clinical trials database (*clinicaltrials.gov*) using "cancer AND exosome AND mesenchymal" to identify relevant clinical trials, and retrieved 14 results. The results were screened manually to determine whether any met the exclusion criteria above, and 5 trials were excluded. We searched the Chinese clinical trials database (*chictr.org.cn*) using "cancer" as the keyword in the public title and "exosome" as the keyword in the scientific title, and 34 results were retrieved. The results of each search were screened manually, and all of these trials were excluded. Therefore, a total of 9 clinical trials were included. All authors participated in the screenings of published articles and clinical trial descriptions, with disagreements resolved by discussion and consensus.

3. Exosome biogenesis and intercellular transfer

Having become a major focus of research over the past decade, studies continue to reveal more information regarding the complex roles exosomes play in intercellular communication, tissue regeneration, and cancer (*28-31*). Almost all human cell types are capable of producing exosomes, and MSCs produce exosomes *via* the same pathways used for exosome production in differentiated cell types (*32*). Figure 1 represents exosome production, exosome release, and exosome internalization. The production of exosomes and the transfer of their molecular cargo allow cells to influence the growth and physiological state of other cells through biochemical signaling. Much of the details of exosome biogenesis and the regulation of its complex pathways lie outside the scope of our review. Herein, we provide a summary of those features relevant to the application of MSC-Exos to the treatment of solid tumors.

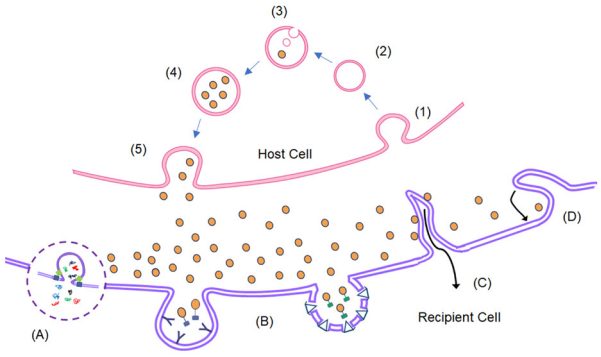

Figure 1. Features of exosome biogenesis and intercellular transfer. Exosome biogenesis is initiated by (1) invagination of the plasma membrane that ultimately forms (2) the early endosome. During endosome maturation, various biomolecules (yellow) are sorted into intraluminal vesicles (ILVs), which are visible in (3) the late endosome. The accumulation of ILVs marks the formation of (4) the multivesicular body (MVB). The MVB fuses with the plasma membrane of the host cell, and (5) scission of the limiting membrane releases the ILVs into the extracellular space as exosomes. The internalization of exosomes into recipient cells can occur by (A) direct-contact membrane fusion (magnified inset), (B) receptor-mediated endocytosis facilitated by clathrin or caveolin, (C) filopodia-mediated endocytosis, or (D) macropinocytosis.

3.1. Exosome production and secretion

Exosomes are produced and released from host cells under homeostatic and pathological conditions *via* constitutive and inducible pathways. Inducible exosome secretion is activated by various stimuli, including heat shock, hypoxia, DNA damage, increased intracellular calcium, and lipopolysaccharide exposure (*33*). Exosome biogenesis is initiated by invagination of the plasma membrane (PM) progressing to form an intracellular vesicle with a phospholipid bilayer membrane known as the early endosome. Pathways known to produce endosomes include caveolin-dependent endocytosis (*34*), clathrin-mediated endocytosis (*35*), and a less-understood third pathway occurring independent of both caveolin and clathrin (*36*). In the late endosome, asymmetric distribution of cell membrane lipids, especially ceramide and cholesterol, contribute to membrane curvature in another invagination process (*37-40*) in which the endosomal sorting complex required for transport (ESCRT) proteins drive further inward bulging and membrane fission to form the intraluminal vesicle (ILV) (*41*), which is simultaneously loaded with biochemical cargo. Upon formation of multiple ILVs, the late endosome is known as the multivesicular body (MVB). Exosome secretion occurs as the MVB fuses with the host cell membrane during exocytosis, and the ILVs become exosomes upon release into the extracellular space, as reviewed by Arya *et al*. (*42*).

Despite the lack of an international consensus, a number of proteins have been identified as exosome markers, with a list of key proteins including CD9, CD63, CD81, tumor susceptibility gene 101, apoptosis-linked gene 2-interacting protein X (Alix), ADP ribosylation factor 6 (Arf6), Flotillin, and the heat shock proteins Hsp70 and Hsp90 (*43,44*). MSC-Exos also carry the MSC-specific markers CD29, CD73, CD90, CD44, and CD105 (*45*). The tetraspanins CD9, CD63, and CD81 function in molecular cargo sorting and cell adhesion. Alix and tumor susceptibility gene 101 function in ILV formation (*46*). Arf6 functions in the formation of ILVs, cargo sorting, and exocytosis. Flotillins function in membrane trafficking, and HsP80 and HsP90 function as molecular chaperones, protecting the secondary and tertiary structures of trafficked proteins (*47*).

RabGTPases function as molecular switches in intracellular transport that allow shifting between different downstream pathways (*48*). Rab7 mediates the transport of endosomes along cytoskeleton fibers in early and late endosome development (*49*), and contributes to multiple steps in endosome development and trafficking (*50*). Three different pathways mediated by RabGTPases are known to contribute to exosome secretion. Rab11 mediates secretion *via* a ubiquitin-dependent ESCRT pathway (*51,52*). Rab27 mediates a ubiquitin-independent ESCRT pathway (*52,53*), in which Rab27 mediates fusion of the MVB with the PM (*54,55*). Rab31 mediates a third pathway in which ceramides and cholesterol associate with Flotillins to recruit Rab31 to late endosomes, resulting in exosome secretion *via* a Rab27-mediated ESCRT-independent pathway (*56,57*). Attachment of the MVB to the PM is mediated by Rab27 and Rab35 (*55,58*). Rab5 and Rab13 mediate the secretion of ILVs as exosomes (*59,60*) with ARF6 mediating membrane remodeling at the site of MVB attachment/fusion through ATP-dependent contraction of actin-myosin fibers in membrane fission (*54,61*).

Though the regulatory mechanisms of these pathways have not been fully elucidated, key elements have been identified, and alterations in one pathway are known to influence the activity of others. Rab5 is required for early endosome formation (*62*), and the transition from early to late endosome is regulated by Rab5 and Rab7, with Rab7 remaining localized with the endosome/MVB through subsequent steps in exosome development (*49*). The recruitment of the TBC1D2B protein by Rab31 inhibits the activity of Rab7 (*56*). While Rab7 is required for Rab27 mediated exosome secretion *via* the ubiquitin-independent ESCRT pathway (*63*), the inhibition of Rab7 also blocks lysosome-MVB fusion (*50*), which shifts the fate of the pathway away from autophagy and toward Rab27 mediated exosome secretion occurring independent of ESCRT pathways (*56*), demonstrating a link between the secretion and recycling pathways.

Though much has been learned regarding exosome biology as presented above, significant variation in exosome biogenesis has been shown to occur based on host cell type and physiological state, with differences in the activities RabGTPases contributing substantially to the variation observed (*57,64,65*). Examples of such variations are exemplified in the results of one study which found that Rab27a and Rab27b functioned in different steps of exosome secretion in squamous carcinoma cells (*55*), whereas studies of human umbilical vascular endothelial cells and bone marrow (BM)-derived mast cells found that Rab27b mediated exosome secretion while Rab27a did not (*64,65*). Such variation is likely influenced by host-specific differences in the predominating secretory pathway, and highlights the overlapping roles of RabGTPases in MVB formation, vesicular secretion, and lysosomal degradation.

3.2. Exosome cargo sorting

The transfer of ILV molecular cargo from host cell to recipient cells is the means by which exosomes function in intercellular communication. The molecular cargo profile of exosomes varies based on host cell type (*66*) and physiological status (*67*). Unique cell-of-origin protein and nucleic acid profiles often remain identifiable in exosomes produced by malignant cells, a property that has led to a great deal of research investigating the use of exosomes as diagnostic markers for cancers originating from a wide range of cell types (*68,69*). Though a

clear understanding of the pathways and regulatory mechanisms involved in cargo sorting is lacking (*42*), a vast array of cargo molecules and key components of the cargo sorting machinery have been identified. Most exosomal cargo sorting appears to occur during ILV production, with lipid- and protein-mediated mechanisms contributing to both processes.

Exosomal cargo can consist of a wide variety of hormones, lipids, cytokines, chemokines, growth factors, extra-nuclear and mitochondrial DNA, messenger RNA, and various non-coding RNAs, including small nuclear RNA, microRNA (miRNA), circular RNA (circRNA), PIWI-interacting RNA, and long non-coding RNA (lncRNA) (*33,70*). Consequently, though the basic physical structure of exosomes is homologous across different cell types, the lipid, protein, and nucleic acid profiles of exosomes from a single cell can vary greatly. The lipid bilayer structure of the exosomal membrane protects the cargo from degradation by sequestering it away from the proteases, lipases, and nucleases commonly found in the extracellular environment, and the self-proteins embedded in the membrane aid in preventing its destruction by host immune cells.

3.2.1. Lipid cargo sorting

Lipids play a key role in the formation of the physical structure of endosomes and ILVs, as well as contributing to exosome function (*37,38*). The ILV membranes contain a variety of lipids, with cholesterol, sphingomyelin, phosphatidylcholine, and phosphatidylserine, being most abundant (*38,71*). Most research regarding endosomal lipids has focused on enrichment of cholesterol. The oxysterol binding protein related protein 1L and steroidogenic acute regulatory protein related lipid transfer domain protein are known to mediate the transfer of cholesterol from the endoplasmic reticulum (ER) to the endosome (*72,73*). In a recent study, CD63 was shown to mediate the sorting of cholesterol into ILVs, resulting in significant cholesterol enrichment (*74*). Flotillins associate with cholesterol in lipid rafts in the cell membrane, which participate in endocytosis (*75*). Flotillins are also associated with cholesterol in ILVs, but the sorting mechanism through which this occurs remains unclear (*76*). Lipid enrichment of the ILV membrane increases lipophilicity, thereby enhancing the fusion of exosomes with recipient cell membranes (*77,78*).

3.2.2. Protein cargo sorting

Cargo proteins are trafficked from the *trans*-Golgi network (TGN) to the endosome, with the proteins involved in cargo sorting arising from the TGN as well (*79*). Important mediators of the endosomal cargo sorting of proteins include ESCRT-0, -I, -II, and -III. The subunits of these ESCRT proteins bind in sequential fashion to the limiting membrane of newly forming endosomes (*41*). ESCRT-0, -I, and -II subunits contain ubiquitin-binding domains that are used to sort ubiquitinated proteins in ILVs (*80*). Though some of these proteins are de-ubiquitinated in the endosome, approximately 15% of exosomal proteins can remain ubiquitinated (*81*). Other post-translational modifications that have been implicated in ESCRT-dependent sorting include myristoylation, ISGylation, glycosylation, and SUMOylation (*82,83*). Following translation on the ER, these modifications occur in the TGN, with ESCRT recognition resulting in sorting into developing ILVs (*84*). Other proteins sorted in ESCRT-dependent secretion include Programmed cell death protein ligand 1(PD-L1) (*85*), Major Histocompatibility Complex II (MHC II) (*86*) , CD63, Syntenin, Syndecan 1 (*63*), β-Integrin (*87*), Fibronectin (*88*), and Protease-activated receptor-1 (PAR1) (*89*).

Less is known regarding protein cargo sorting in ESCRT-independent exosome secretion. The lysosome-associated membrane protein 2 isoform A (LAMP2A) protein binds the KFERQ consensus peptide motif in other proteins, which account for approximately 20% of membrane proteins in the human proteome. A recent study showed that LAMP2A mediates the sorting of KFERQ-containing proteins into early endosomes, ultimately localizing to ILVs and being secreted *via* the Rab31-mediated pathway (*90,91*). This cargo sorting mechanism requires the cytosolic KFERQ binding protein HSC70, as well as CD63, Alix, Syntenin-1, and ceramides, and results in Flotillin enrichment (*91*). Flotillins associate with cholesterol and ceramide rich membranes (*92*), and recruit Rab31 in early endosome production (*56*). LAMP2A-mediated sorting also enriches exosomes with the hypoxia-inducible transcription factor 1 α (HIF1A) protein (*91*), which contains the KFERQ motif (*93*). HIF1A is upregulated in cells under hypoxic conditions that are known to contribute to resistance to anti-cancer treatments in solid tumors (*94*). A separate study found that EGFR, which also contains the KFERQ motif (*95*), was enriched in exosomes produced *via* the Rab31-mediated pathway (*56*).

Exosomes are enriched with the tetraspanins CD9, CD37, CD63, CD81, and CD82 (*96*), with CD63 being the most abundant regardless of the biogenesis pathway used (*97,98*). Despite the abundance of tetraspanins in exosomes, their contributions to protein sorting in exosome biogenesis are largely unclear. CD63 is trafficked to early endosomes in ESCRT-dependent exosome production, yet is required for ESCRT-independent LAMP2A-Rab31-mediated secretion (*91*). In a recent study, investigators showed that CD9 inhibited the localization of CD63 to early endosomes in ESCRT-independent exosome production (*99*). Further experiments showed that the CD9-mediated reduction of CD63 localization was reversed by blocking endocytosis using three separate inhibitors with different mechanisms

of action (*99*). Proteins that are sorted into ILVs by tetraspanins *via* ESCRT-independent pathways include CD10, β-Catenin, Ezrin, RAC (*96*), PD-L1 (*85*) PMEL17 (*100*), and LMP1 (*101*). Exosomes are also enriched with HSP70, HSP90, and HSP20, but the mechanism by which these are sorted is not clear.

3.2.3. Nucleic acid cargo sorting

Double-stranded genomic DNA (*102*), single-stranded DNA (*103*), mitochondrial DNA (*103*), and viral DNA (*104*) have been identified in exosomes. DNA molecules have been identified both encapsulated and exposed on the surface of exosomes (*104*). The sorting mechanisms and functions of exosomal DNA remain unclear, and it is the least studied aspect of endosomal trafficking in cells under homeostatic conditions. Exosomes can also contain a wide variety of cellular RNA molecules including mRNAs, lncRNAs, sRNAs, miRNAs, circRNAs, PIWI-interacting RNA, vault RNAs (vtRNAs), Y RNAs, transfer RNA fragments, small nucleolar RNAs (snoRNAs), ribosomal RNA fragments, and mitochondrial RNAs (*105,106*). Despite the wide variety of RNA species that have been identified in exosomes, relatively little is known regarding the mechanisms by which these molecules are sorted into exosomes. Passive RNA loading is dependent on the intracellular concentration of RNAs. Though selective sorting of RNAs are active processes, the quantity of molecules sorted into exosomes is also influenced by the intracellular concentration of the RNA species involved .

The sorting of many RNAs has been shown to be mediated, at least in part, by sequence motifs contained within them. Exosomes are enriched with miRNA containing the CGGGAG sequence motif, whereas miRNAs with AUUA, AGAAC, and CAGU motifs are most often limited to cells (*107*). In addition, miRNA isoforms with 3' uridylation are over-represented in exosomes (107). The sorting of mRNAs into exosomes is likely mediated by the primary and secondary structures of the transcript. A 25 nucleotide sequence was found to be enriched in exosomal mRNAs. This sequence forms a stem-loop structure which contains a core CUGCC sequence and an miR-1289 binding site (*108*). However, many of the exosomal mRNA containing these motifs have been found to exist as non-functional fragments of transcripts, and their function in recipient cells is unclear (*109*). The enrichment of exosomes with circRNAs has been proposed to be mediated by the GMWGVWGRAG degenerate sequence motif in hepatoma cells (*110*). At least 21 RNA motifs have been identified that mediate the sorting of RNAs by association with lipid rafts in the limiting membrane of developing ILVs, constituting a passive RNA-specific sorting mechanism (*111*).

A number of heterogeneous nuclear ribonucleoproteins (hnRNPs) have been identified that mediate the sorting of miRNAs with specific motifs, including the following hnRNPs and motif sequences: hnRNPA2B1 (GGAG, AGG, UAG or A/G-rich sequences); hnRNPK (UC_3–$4[U/A]_2$); hnRNPC1 (AU-rich sequences); hnRNPG (CC[A/C]-rich); hnRNPH1 (GGGA); and hnRNPQ (GGCU, AYAAYY, or UAUYRR) (*107,109,112*). The sorting of lncRNAs has also been shown to be mediated by hnRNPA2B1 in a number of cancer cell lines (*110,113,114*). This sorting mechanism is dependent on the GGAG motif in the lncRNAs in at least some of these cells (*115*). At least 14 other proteins that function in other cellular processes have also been shown to contribute to the sorting of exosomal RNAs, as reviewed in Fabbiano *et al*. (*112*). Nine of these do so through the recognition of RNA sequence motifs. Among these is the Argonaut 2 (AGO2) protein, which functions in the miRNA induced silencing complex (miRISC)-related pathway, and mediates sorting through the recognition of GCACUU and G-rich sequences in various RNAs, such as miR-320a, miR-100, and miR-let-7a (*116*). One of the RNA sorting proteins for which an RNA motif has not been detected is Alix, an exosome biomarker that also functions as an ESCRT accessory protein in ILVs (*117*). Alix has been shown to contribute to the sorting of miR-24, miR-31, miR-125b, miR-99b, miR-221, miR-16, and miR-451 (*118*).

3.3. Exosome uptake

Fusion of the MVB with the PM of the host cell and scission of the limiting membrane of the MVB results in the release of ILVs into the extracellular space as exosomes. Upon contact with other cells, integrins in the exosome membrane interact with recipient cell adhesion molecules to facilitate attachment (*119*). Exosomal membrane proteins can stimulate phagocytosis by immune cells and influence immuno-surveillance *via* the detection of antigens presented in MHC proteins in the exosome membrane (*120*). Exosomal membrane surface proteins may act as ligands interacting with cell-surface receptors of the recipient cell, which can contribute to the target-cell specificity demonstrated by exosomes *in vivo* (*121*). Such interactions may also result in juxtacrine transduction of signaling pathways (*122*) or localize exosomes to sites of endocytosis machinery in the PM of the recipient cell (*123*).

As shown in Figure 1, the internalization of exosomes into recipient cells can occur by (A) direct-contact membrane fusion (*124*), (B) receptor-mediated endocytosis facilitated by clathrin or caveolin (*125,126*), (C) filopodia-mediated endocytosis (*119,127*), or (D) macropinocytosis (*126*). Though membrane fusion mediated uptake results in the release of exosomal molecular cargo (Figure 1, magnified inset), endocytosed exosomes remain intact and are encapsulated in endosomes. The fate of internalized endosomes is primarily dictated by the cell type and physiological state of the recipient cell, but the various mechanisms

involved are poorly understood. These endosomes may fuse with lysosomes for degradation or antigen processing, or may become permeabilized by recipient cell lipases (*128*). Encapsulated exosomes can fuse with the limiting membrane of the endosome (*127,129*), but it is not entirely clear whether this releases exosomal cargo (*128*). The endosome may localize to the ER, making the exosomal cargo available for trafficking elsewhere within the recipient cell, but evidence of this is lacking. Alternatively, the encapsulated exosomes and functional cargo may be secreted by the recipient cell (*130*).

4. Effects of MSC-Exos on cancer cells and potential therapeutic effects

MSCs primarily exert their regulatory functions through paracrine pathways, and MSC-Exos have been implicated in various tumor-related processes, including tumor cell proliferation, apoptosis, metastasis, and treatment resistance (*131,132*). Studies using MSC-Exos for miRNA delivery have reported both the enhancement and inhibition of tumor cell proliferation, with one such study reporting that miR-130b-3p, promoted cell proliferation, migration, and invasion in human lung cancer cell lines (*133*). Similar tumorigenic effects have been observed in other types of malignant tumors, including renal, breast, and nasopharyngeal cancers, where specific miRNAs within MSC-Exos contributed to carcinogenesis (*23*). *In vitro* studies have demonstrated that BM-derived MSCs (BM-MSCs) enhance vascular endothelial growth factor (VEGF) expression in tumor cells, activating the extracellular signal-regulated kinase 1/2 (ERK1/2) pathway to exert pro-cancer effects (*134*). Factors present in exosomes, such as cytokines and adhesion molecules, may also promote tumor development, as reviewed in Moeinzadeh *et al*. (*135*).

By contrast, MSC-Exos have also demonstrated anti-cancer properties. The IRF2/INPP4B pathway, which promotes apoptosis in acute myeloid leukemia cells, was inhibited by BM-MSC-Exos carrying miR-222-3p (*136*). Exosomes produced by human adipocyte (AT)-derived MSCs (hAT-MSC-Exos) and umbilical cord-derived MSCs (hUC-MSC-Exos) also demonstrate anti-cancer effects. The delivery of miR-145 by AT-MSC-Exos was shown to inhibit prostate cancer cell proliferation by reducing Bcl-xL activity and promoting apoptosis through the caspase-3/7 pathway (*137*). Furthermore, MSC-Exos are linked to the epithelial-to-mesenchymal transition (EMT), enhancing tumor cell migration and invasion (*138*), and hUC-MSC-Exos have been shown to induce EMT *via* the ERK pathway in breast cancer cells, contributing to tumor progression and metastasis (*139*).

MSC-Exos have also been shown to promote angiogenesis in mouse model experiments by inducing vascular endothelial growth factor (VEGF) expression and stimulating MSC-Exos-mediated cell-cell interactions that contribute to tumor progression (*140*). A previous study demonstrated that exosomes isolated from the conditioned medium of BM-MSCs can transfer various pro-angiogenic miRNAs to human umbilical vein endothelial cells *in vivo*, thereby enhancing angiogenesis and facilitating communication between stem cells and endothelial cells (*141*). Wnt proteins are potent angiogenic factors, and their signaling pathways significantly influence angiogenesis and vascular remodeling. MSC-Exos have been shown to stimulate fibroblast proliferation and promote angiogenesis *in vitro* (*142*). The anti-vascular remodeling properties of MSC-Exos have been corroborated by several studies. One such study revealed that exosomal miR-16, which is enriched in MSC-Exos, inhibits angiogenesis in breast cancer cells by downregulating VEGF and CD31 expression and modulating the *mTOR/HIF-1α/VEGF* signaling axis (*143,144*).

MSC-Exos possess immunomodulatory capabilities similar to those of MSCs. Functioning not only as natural antigen carriers, but also act as antigen presenters, MSC-Exos regulate both direct and indirect antigen presentation to stimulate both adaptive and innate immune responses. Furthermore, exosomes facilitate the transfer of antigenic peptides or bioactive molecules, thereby influencing other immune cell subpopulations (*145*). Notably, BM-MSC-Exos have been shown to downregulate interferon (IFN)-γ expression in dendritic cells (DCs) and T cells (*146*). Other research has also indicated that BM-MSC-Exos can activate immature DCs, leading to increased secretion of IL-10, increased numbers of $Foxp3^+$ regulatory T cells (Treg), and the inhibition of inflammatory T helper cell responses (*147*). MSC-Exos derived from other sources also play roles in immune regulation. AT-MSC-Exos have been reported to inhibit the proliferation and activation of stimulated T cells (*148*), while hUC-MSC-Exos induce the expression of immunosuppressive cytokines through interactions with peripheral blood monocytes, which promotes the development of M2 macrophages (*149*).

Chemotherapy remains a cornerstone treatment for many solid tumors, yet the emergence of multidrug resistance in tumor cells presents a significant challenge to its efficacy. To develop effective strategies that can overcome this resistance, understanding its underlying mechanisms is essential. Recent evidence suggests that MSC-Exos play a pivotal role in promoting treatment resistance (*150*). Ji *et al*. (*151*) demonstrated that MSC-Exos can enhance tumor cell resistance to 5-fluorouracil *in vitro* and *in vivo* by activating the CaM-Ks/Raf/MEK/ERK signaling cascade and modulating MDR-related proteins, thereby preventing apoptosis. Furthermore, tumor dormancy, the process wherein cancer cells in metastatic sites remain in the G0 phase after the primary tumor's removal, is strongly linked to cancer recurrence, metastasis, and chemotherapy resistance. Phan and Croucher (*152*) have suggested that MSC-Exos from cancer cells can induce dormancy, which contributes

to cisplatin resistance. By contrast, MSC-Exos have also been shown to increase chemotherapy sensitivity in various types of cancer (*23*). Though AT-MSC-Exos have been shown to reverse cisplatin resistance in breast cancer cells (*153*), hUC-MSC-Exos have been shown to restore sensitivity to docetaxel and paclitaxel by regulating LAMC2 expression and the PI3K/Akt signaling pathway (*154*).

The EMT has also been implicated in chemotherapy resistance, and inhibiting the EMT represents a promising strategy for resistance reversal. Treatment with hUC-MSC-Exos containing miR-451a has been shown to suppress EMT *in vitro* by inhibiting disintegrin-metalloproteinase-10 (ADAM10) protein expression, thereby increasing the sensitivity of tumor cells to paclitaxel (*155*). Targeted therapies have been developed in which antibodies are used to target specific molecular pathways involved in chemoresistance. These include cetuximab and panitumumab, which target epidermal growth factor receptor (EGFR), as well as trastuzumab, which targets HER-2 (*156,157*). However, despite the significant improvements these therapies offer, resistance remains a major obstacle to long-term survival. MSC-Exos have been implicated in mediating resistance to targeted therapies. For example, changes in the contents of BM-MSC-Exos produced by acute myeloid leukemia malignancy have correlated with resistance to tyrosine kinase inhibitors (*158*). However, in chronic myeloid leukemia, treatment with hUC-MSC-Exos enhanced sensitivity to the tyrosine kinase inhibitor imatinib by promoting apoptosis through the activation of caspase-9 and caspase-3 (*159*).

The exploration of immune factors in the TM has opened new possibilities for immunotherapy, which directs the immune system to target cancer cells to promote cell cycle progression regulation, cell death, and the inhibition of metastasis and angiogenesis (*25,160*). However, a significant proportion of patients fail to respond to immunotherapy due to primary, adaptive, or acquired resistance (*161*). Recent research suggests that exosomes play an immunomodulatory role in the TM by influencing the activity of natural killer cells, T cells, and B lymphocytes (*162*). MSC-Exos have been shown to modulate immune cell functions, and alter the secretion of inflammatory factors, such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β. In one study, MSC-Exos promoted the differentiation of monocytic myeloid-derived suppressor cells into immunosuppressive M2 macrophages (*163*). Future studies are needed to clarify whether MSC-Exos have an overall immunosuppressive or immuno-stimulatory role in the TM, and to establish how they might influence resistance to immunotherapy. In pancreatic ductal adenocarcinoma (PDAC), BM-MSC-Exos carrying galectin-9 small interfering RNA (siRNA) and oxaliplatin prodrugs have been found to induce immunogenic cell death, and reverse immunosuppression in the TM by reducing M2 macrophage polarization and recruiting cytotoxic T lymphocytes, suggesting that enhancement of immunotherapy (*164,165*).

MSC-Exos have also gained attention as promising carriers for biomolecules and chemical agents in solid-tumor malignancies due to their role intracellular communication, low immunogenicity, minimal toxicity, high bioavailability, evasion of immune cell phagocytosis, and potential to cross biological barriers, as review by Lin *et al*. (*23*). Engineered MSC-Exos can encapsulate therapeutic miRNAs, proteins, and drugs, offering novel therapeutic avenues. Mechanistically, MSC-Exos can deliver specific miRNAs that promote caspase activity and induce apoptosis by inhibiting the expression of drug efflux proteins, such as the multidrug resistance-1 (MDR1) protein (*166*). In addition, MSC-Exos provide a platform for delivering siRNAs, enhancing drug sensitivity and therapeutic outcomes in various cancer treatments (*167*). Their potential in chemotherapy drug delivery is also significant, as MSC-Exos can improve the effects of drugs inhibiting tumor growth and improve tumor site targeting precision compared to that of traditional chemotherapy (*168*). Furthermore, MSC-Exos can cross critical physical barriers, such as the blood-brain barrier, likely by endocytosis, thus facilitating the delivery of therapeutic drugs and thereby increasing chemotherapy drug concentrations in challenging tumor site locations, as reviewed by Sen *et al*. (*169*). We have included a summary of our discussion of the effects of MSC-Exos and miRNAs on solid tumor malignancies in Figure 2.

4.1. Breast cancer

Recent studies have highlighted the multifaceted role of MSC-Exos in breast cancer, particularly in influencing angiogenesis, cell proliferation, migration, immune evasion, and chemotherapy resistance. MSC-Exos regulate angiogenesis primarily through the delivery of specific miRNAs. Treatment with BM-MSC-Exos containing miR-16 reduces VEGF expression, which inhibited angiogenesis and tumor progression in 4T1 breast cancer cells (*143*). Further research also demonstrated that treatment with BM-MSC-Exos carrying miR-100 downregulated VEGF expression by modulating the *mTOR/HIF-1α* axis, which also suppressed angiogenesis *in vitro* (*170*).

In addition to their role in angiogenesis, MSC-Exos also exhibit anti-tumor properties by regulating gene expression. Treatment with MSC-Exos containing miR-148b-3p and miR-145 inhibited breast cancer cell proliferation by downregulating the expression of the oncogenes *erb-b2 receptor tyrosine kinase 2* (*ERBB2*), *tripartite motif containing 59* (*TRIM59*), *matrix metallopeptidase 9* (*MMP9*), *Rho associated coiled-coil containing protein kinase 1* (*ROCK1*), and *tumor protein p53* (*TP53*) oncogenes (*171*). The treatment of the breast cancer cell line MCF-7 with MSC-Exos containing

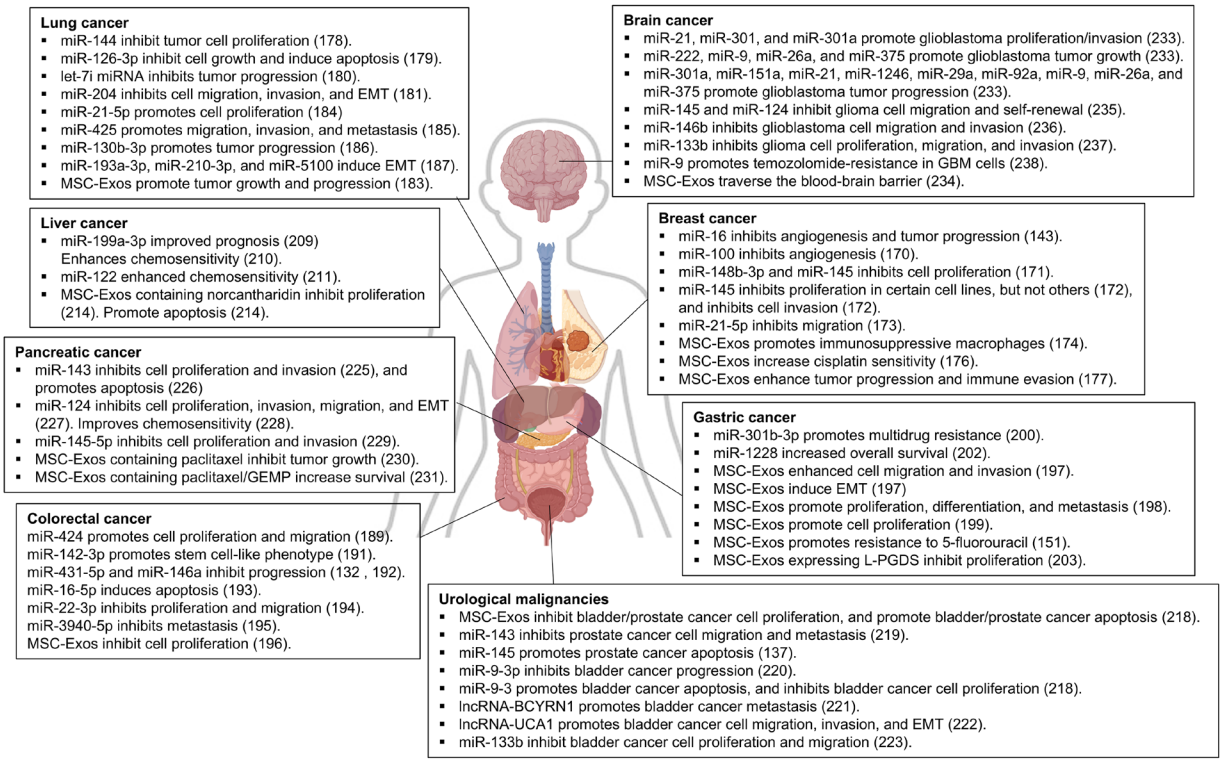

Figure 2. Visual summary of the effects of mesenchymal stromal cell-derived exosomes (MSC-Exos) and non-coding RNAs on solid tumor malignancies. The effects of various miRNAs, lncRNAs, and MSC-Exos on brain cancer, lung cancer, breast cancer, liver cancer, gastric cancer, colorectal cancer, pancreatic cancer, and urological malignancies are presented to summarize both the pro-tumor and anti-tumor effects of each, as discussed in section *4. Effects of MSC-Exos on cancer cells and potential therapeutic effects*.

miR-145 inhibited *membrane mucin-1* (*MUC1*) gene expression, which is closely associated with metastasis, and suppressed cell growth. By contrast, miR-145 did not suppress cell growth in the synonymous breast cancer cell lines MDA-MB-231 and LM2-4142, but it did inhibit cell invasion in both (*172*). Similarly, MSC-Exos inhibited *zinc finger protein 367* (*ZNF367*) gene expression through a miR-21-5p-mediated mechanism, which suppressed the migration of breast cancer cells (*173*). These findings suggest that MSC-Exos containing selected miRNAs can regulate multiple pathways to contribute to the inhibition of tumor progression and metastasis.

MSC-Exos can contain immune-regulatory factors, including transforming growth factor (TGF)-β, that influence various signaling proteins that drive *Programmed cell death 1 ligand 1* (*PD-L1*) gene overexpression in BM monocyte precursors. This leads to the differentiation of immunosuppressive macrophages, creating a tumor-favorable immune environment that ultimately accelerates cancer progression (*174*) by contributing to the immune evasion properties of breast cancer cells (*175*). These results demonstrate the importance of PD-L1 inhibition as a target for enhancing anti-tumor immunity in breast cancer. In addition, MSC-Exos have been shown to increase cisplatin sensitivity by downregulating *solute carrier family 9* (*SLC9A1*) gene expression and inactivating the Wnt/β-catenin pathway in breast cancer cells, representing a possible means of overcoming chemotherapy resistance (*176*). However, the effects of MSC-Exos on breast cancer progression is context-dependent, and their effects can vary based on the cell type of origin. For instance, though hUC-MSC-Exos inhibit breast cancer development, AT-MSC-Exos enhance tumor progression and immune evasion (*177*). These results underscores the need to further characterize the properties of exosomes produced by MSC derived from different source cell-types in order to bolster the development of MSC-Exo based therapeutics for breast cancer.

4.2. Lung cancer

Understanding the role of MSC-Exos in lung cancer is crucial, as these exosomes significantly influence the development and progression of this aggressive malignancy. Advances in this field could pave the way for new therapeutic strategies. BM-MSC-Exos carrying miR-144 have been shown to target the cell cycle proteins cyclin E1 (CCNE1) and cyclin E1 (CCNE2), which inhibited colony formation and the proliferation of lung cancer cells (*178*). Exosomes rich in miR-126-3p have been shown to suppress lung cancer cell growth and induce apoptosis by downregulating non-receptor

protein tyrosine phosphatase 9 (PTPN9) (*179*). The let-7i miRNA inhibits lung cancer progression through the *KDM3A/DCLK1/FXYD3* axis, which functions in the regulation of ion transport (*180*), and MSC-Exos containing miR-204 inhibit cell migration, invasion, and the EMT in lung cancer cells *via* the *KLF7/AKT/HIF-1α* axis (*181*). MSC-Exos containing specific circRNA or miRNAs, such as circRNA-100395, miR-631, miR-598, and miR-320A, also exhibit potent anti-tumor effects, as review by Feng *et al*. (*182*).

MSC-Exos have also been shown to contribute to the lung cancer microenvironment through processes that support tumor growth and progression (*183*). MSC-Exos enriched with miR-21-5p suppress *SMAD7* gene expression thereby promoting lung cancer cell proliferation (*184*). Treatment with BM-MSC-Exos containing miR-425 suppresses *cytoplasmic polyadenylation element binding protein 1* (*CPEB1*) gene expression, which contributes to cell migration, invasion, and lung metastasis in lung cancer cells (*185*). Treatment with hUC-MSC-Exos enriched with miR-130b-3p also promote lung cancer progression through the *FOXO3/NRF2/TXNRD1* axis in the human lung cancer cell lines H292 and H1299 (*186*), and hypoxic BM-MSC-Exos containing miR-193a-3p, miR-210-3p, and miR-5100 induced the EMT *in vivo* in a mouse syngeneic lung cancer tumor model by activating the signal transducer and activator of transcription 3 (STAT3) signaling pathway, which promotes invasion and metastasis in lung cancer (*187*). These results highlight potential targets for MSC-Exo based therapeutics in future studies.

4.3. Colorectal cancer

Studies have reported that MSC-Exos can promote the tumor proliferation, migration, and invasion properties of colorectal cancer cells through the delivery of specific miRNAs (*188*). MSC-Exos carrying miR-424 enhance colorectal cancer cell proliferation and migration, while inhibition of miR-424 induces apoptosis in colorectal cancer cell lines (*189*). The expression of miR-424 and TGFBR3 are linked to tumor differentiation, infiltration depth, TNM staging, vascular invasion, lymph node metastasis, and distant metastasis, making miR-424 a potential therapeutic target for the treatment of colorectal cancer (*190*). MSC-Exos delivering miR-142-3p promote a stem cell-like phenotype in colorectal cancer cells, thereby exacerbating disease progression (*191*). The results of these studies highlight the value of these miRNA as potential targets for MSC-Exo based therapies through the enrichment of MSC-Exos with siRNAs designed to silence the expression of miR-424 and miR-142-3p.

MSC-Exos enriched with certain other miRNAs can exhibit inhibitory effects on colorectal cancer. MSCs containing miR-431-5p have been shown to suppress colorectal cancer progression by downregulating *peroxiredoxin 1* (*PRDX1*) gene expression (*192*), and MSC-Exos containing miR-16-5p were shown to selectively suppress the expression of integrin subunit alpha 2 (ITGA2) mRNA, inducing apoptosis in colorectal cancer cells (*193*). In addition, miR-22-3p in MSC-Exos has been shown to downregulate expression of the *RAS* family oncogene *RAP2B*, which inhibited the PI3K/AKT signaling pathway, reducing both the proliferation and migration of colorectal cancer cells (*194*). MSC-Exos containing miR-3940-5p have been shown to inhibit colorectal cancer metastasis by inhibiting *integrin α6* (*ITGA6*) gene expression (*195*), whereas the miR-146a/*SUMO1* axis contributes to both the alleviation of colitis and inhibition of colorectal cancer progression (*132*). MSC-Exos also suppress the expression of aquaporin-5 and EGFR proteins in colorectal cancer cell lines (*196*). These results highlight the value of specific miRNAs as promising therapeutic targets for MSC-Exo based treatments for colorectal cancer.

4.4. Gastric cancer

Gu *et al*. (*197*) found that treatment with hUC-MSC-Exos enhanced cell migration and invasion in the HGC-27 gastric cancer cell line by inducing the EMT through activation of Akt pathway signaling. In another study, hBM-MSC-Exos promoted proliferation, differentiation, and metastasis in MG63 and SGC7901 gastric cancer cell lines by activation of the Hedgehog signaling pathway (*198*). Later, Chen *et al*. (*199*) found that conditioned media containing hBM-MSC-Exos promoted gastric cancer cell proliferation by increasing the expression of the retroviral oncogene *c-Myc* in the MGC-803 and BGC-823 gastric cancer cell lines. These findings suggest that MSC-Exos could serve as promising therapeutic targets for the treatment of gastric cancer.

Research has highlighted the role of MSC-Exos as a key mediator of chemotherapeutic drug resistance in gastric cancer. Ji *et al*. (*151*) showed that hUC-MSC-Exos induced resistance to 5-fluorouracil in HGC-27, MGC-803, and SGC-7901 gastric cancer cell lines and a subcutaneous xenograft tumor model in mice by increasing the expression of the multidrug resistance genes *ATP-binding cassette, sub-family B member 1A* (*P-gp*/*MDR*), *ATP-binding cassette, sub-family C member 1* (*MRP*), and *major vault protein* (*LRP*). *In vitro* experiments showed that treatment with hUC-MSC-Exos activated calcium/calmodulin-dependent protein kinases (CaM-Ks) and the Raf/MEK/ERK kinase cascade in the gastric cancer cell lines. Treatment with MSC-Exos containing miR-301b-3p was also shown to promote drug resistance by inhibiting the expression of *thioredoxin-interacting protein* (*TXNIP*), which downregulated the expression of *P-gp*/*MDR* and *MRP* in gastric cancer cells (*200*). Targeting the interaction between MSC-Exos and cancer cells may offer novel strategies to improve the effectiveness of chemotherapy for the treatment of

gastric cancer.

MSC-Exos have shown great promise as an efficient nano-carrier for targeted drug delivery in gastric cancer therapy. Preclinical studies have demonstrated that MSC-Exos can deliver miR-1228 into gastric cancer cells, where it inhibits NF-κB activity (*201*). Additional research has revealed that MSC-Exos enriched with miR-1228 reduced gastric cancer cell growth by downregulating *matrix metalloproteinase-14* (*MMP-14*) gene expression, and analysis of serum exosomes showed miR-1228 was associated with increased overall survival in gastric cancer patients (*202*). MSC-Exos engineered to overexpress the *lipocalin-type prostaglandin D2 synthase* (*L-PGDS*) gene have been shown to inhibit the proliferation of SGC-7901 gastric cancer cells by inducing PPARγ expression and suppressing STAT3 phosphorylation (*203*). These results show that MSC-Exos have great potential for the development of an efficient drug delivery system for the treatment of gastric cancer.

Adenocarcinomas are common at both esophageal and gastric sites. Therefore, some MSC-Exos mediated effects on gastric cancer might also apply to esophageal cancer due to similar etiological characteristics (*204*), such as the effects of L-PGDS enriched MSC-Exos on the SGC-7901 gastric cancer cell line, an adenocarcinoma derivative. Though squamous cell carcinoma (SCC) is the most common type of esophageal cancer, the etiology of esophageal SCC is more poorly understood than that of adenocarcinoma (*204*), which might make it less attractive for MSC-Exo-related studies, given that fewer studies of MSC-Exos in esophageal cancer have been performed thus far (*205*). However, studies have shown that the EMT is also induced in esophageal SCC (*206*), and that treatment with hUC-MSC-Exos containing miR-375 promoted apoptosis and inhibited cell proliferation, invasion, migration, and tumorsphere formation in the KYSE70, ECA109, and EC9706 esophageal SCC cell lines (*207*).

4.5. Liver cancer

The acquisition of drug resistance poses a significant challenge for liver cancer treatment, leading to unsatisfactory clinical outcomes and reduced survival, which highlights the urgent need for novel therapies to improve the sensitivity of liver cancer to chemotherapy and targeted treatments. Evidence suggests that exosomal miRNAs have critical functions in liver cancer progression and MDR in hepatocellular carcinoma (HCC) (*208*). Notably, miR-199a-3p has been identified as a regulator of hepatocyte apoptosis and hepatocarcinogenesis, and lower levels of this miRNA has been correlated with poor prognosis in HCC (*209*). Another study showed that AT-MSC-Exos enriched with miR-199a could effectively enhanced the sensitivity of HCC cells to chemotherapy drugs by targeting the mTOR signaling pathway (*210*). A similar study showed that treatment with miR-122 enriched AT-MSC-Exos enhanced the efficacy of 5-fluorouracil and sorafenib treatments in the HepG2 liver cancer cell line (*211*). Therefore, targeting specific miRNA through MSC-Exos has represents a possible strategy for enhancing chemosensitivity in treatments for HCC.

Researchers have also explored the potential of MSC-Exos as functional drug carriers in combination therapies for HCC. Norcantharidin, a demethylated derivative of zebularine, has been shown to inhibit the proliferation and migration of HCC cells when used in combination with 2-deoxyglucose (*212*). Previous studies have demonstrated that conjugating norcantharidin with biomaterials significantly enhanced its therapeutic efficacy against various types of HCC (*213*). Treatment with norcantharidin-enriched BM-MSC-Exos resulted in greater cellular uptake of norcantharidin, which induced cell cycle arrest and reduced tumor proliferation and increased apoptosis of HepG2 cells (*214*). Liang *et al*. (*214*) also found that treatment with norcantharidin-enriched BM-MSC-Exos promoted the repair of damaged non-cancerous L02 hepatocytes. These therapeutic properties of BM-MSC-Exos enriched with key miRNA offers a promising avenue for future cancer therapies.

4.6. Urological malignancies

A previous review highlighted the critical need for more effective therapies for advanced urological cancers (*215*). Studies have proposed advanced strategies to mitigate cancer progression by depleting circulating exosomes in the systemic circulation as a treatment for urological tumors (*216*). Increasing evidence suggests that MSC-Exos can play a therapeutic role, offering distinct advantages over traditional cell therapies (*217*). A recent study evaluated the impact of hAT-MSC-Exos on the 5637 bladder cancer cell line, the LNCaP hormone-sensitive prostate cancer cell line, and the PC3 hormone-refractory prostate cancer cell line, and the results strongly suggested that exosomes exhibited significant changes in the expression of cancer-related genes across all of the cell lines tested (*218*). Though hAT-MSC-Exos increased *tumor protein p53* (*P53*) expression and reduced *BCL2 apoptosis regulator* (*BCL2*) expression in all of the cell lines, the differential expression of other genes was observed across cell lines.

In the 5637 cells, the expression level of *vascular endothelial growth factor A* (*VEGFa*) and *BCL2 associated X apoptosis regulator* (*BAX*) were also significantly reduced by hAT-MSC-Exos treatment. In the LNCaP cells, the expression levels of *VEGFc* and *BAX* were significantly reduced. In PC3 cells, expression levels of the OPNb and OPNc isoforms of the *secreted phosphoprotein 1* (*OPN*) gene were significantly increased, and *BAX* was significantly reduced. Cell

culture experiments showed the hAT-MSC-Exos treatment reduced cell proliferation in all three cell lines, suggesting the hAT-MSC-Exos-induced changes in gene expression exerted apoptotic effects on the bladder and prostate cancer cell lines (*218*). These preclinical findings further suggest that hAT-MSC-Exos might inhibit the occurrence and progression of urological tumors by enhancing cell apoptosis. Future research should provide important findings to support development of MSC-Exo based therapies for urological cancers.

Other studies have shown that exosomal miRNAs play crucial roles in post-transcriptional gene regulation in urological tumors. For instance, studies suggest that treatment with miR-143-enriched BM-MSC-Exos can prevent cell migration and metastasis in prostate cancer (*219*). Preclinical research has also shown that AT-MSC-Exos reduced cell proliferation and induced apoptosis in a tumor xenograft mouse model of metastatic prostate cancer, and cell culture studies showed the apoptotic effect of AT-MSC-Exos resulted from a reduction in BCL2 like 1 (BclxL) protein expression through a mechanism mediated by miR-145 (*137*). These results suggest that miR-145 enriched AT-MSC-Exos represents a novel therapeutic strategy to treat prostate cancer. In another study, treatment with BM-MSC-Exos containing miR-9-3p can inhibit bladder cancer progression by downregulating endothelial cell-specific molecule 1 (ESM1), presenting an additional therapeutic target (*220*). Furthermore, MSC-Exos has been shown to enhance apoptosis and necrosis while inhibiting cell proliferation in the BIU-87, EJ-1, T24, 5637, and UMUC-3 bladder cancer cell lines and a tumor xenograft mouse model of bladder cancer (*218*). Cell culture experiments showed that miR-9-3 mediated the effects of BM-MSC-Exo treatment by reducing *endothelial cell-specific molecule 1* (*ESM1*) gene expression.

Investigations of non-MSC exosomes isolated from bladder cancer patients have shown that exosomal lncRNA-BCYRN1 contributes to bladder cancer metastasis in a mouse popliteal lymph node metastasis model through VEGF-C/VEGFR3 signaling (*221*), and that lncRNA-UCA1 contributes to cell migration, invasion, and the EMT in 5637, T24, and UMUC2 bladder cancer cell lines by inhibiting miR-145 expression and enhancing the expression of *zinc finger E-box binding homeobox 1 and 2* (*ZEB1* and *ZEB2*), which induces the EMT (*222*). In another study, exosomal miR-133b was shown to inhibit cell proliferation and migration in the 5637 and T24 bladder cancer cell lines and inhibited tumor growth in a mouse tumor xenograft model through an increase in *dual-specificity protein phosphatase 1* (*DUSP1*) gene expression (*223*). These results identify additional possible targets for future research in the development of novel treatments for urological malignancies in which MSC-Exos can be enriched with lncRNA-BCYRN1, lncRNA-UCA1, and/or miR-133b.

4.7. Pancreatic cancer

A series of preclinical studies have demonstrated that treatment with MSC-Exos enriched with siRNA specific for the $KRAS^{G12D}$ GTPase, a mutant of the *KRAS* proto-oncogene, resulted in suppressed tumor progression and increased overall survival in a mouse model of pancreatic cancer (*224*). Notably, the expression of miR-143 is significantly decreased in pancreatic cancer (*225*), while treatment with exosomal miR-143 can inhibit cell proliferation and promote apoptosis in a mouse model of pancreatic cancer (*226*) Additionally, miR-143 induces apoptosis in pancreatic cancer cells and inhibits their growth, invasion, and migration by downregulating COX-2 and KRAS (*225*).

In another study, treatment with miR-124 enriched BM-MSC-Exos were shown to inhibit the proliferation, invasion, migration, and EMT of AsPC-1, PANC1, BxPC-3 and SW1990 pancreatic adenocarcinoma (PAC) cell lines and a mouse tumor xenograft model of PA. Cell culture experiments showed that miR-124 reduced *Zeste 2 polycomb repressive complex 2 subunit* (*EZH2*) gene expression, which induced apoptosis in PAC cells (*227*). Treatment with BM-MSC-Exos carrying miR-124 also enhanced the sensitivity of PAC cells to chemotherapy. Additionally, treatment with MSC-Exos containing miR-1231 was shown to inhibit cell proliferation BxPC-3 and MIA PaCa-2 pancreatic ductal adenocarcinoma (PDAC) cell lines and a mouse tumor xenograft model (*228*). These results suggest that MSC-Exos present a promising therapeutic approach for delivering PA-inhibitory miRNAs to pancreatic tumors.

Exosomes can also serve as an attractive nanoscale drug delivery platform, which has been actively explored for the treatment of pancreatic cancer. Researchers have utilized hUC-MSC-Exos to deliver exogenous miR-145-5p *in vitro* and in a mouse model, where it inhibited the proliferation and invasion of PDAC cells, promoted apoptosis and induced cell cycle arrest by reducing *SMAD family member 3* (*Smad3*) gene expression (*229*). In another study, investigators successfully loaded MSC-Exos with the anti-cancer drug paclitaxel, and demonstrated that treatment with paclitaxel-enriched MSC-Exos significantly inhibited tumor growth *in vitro*, which provided the first evidence of active drug encapsulation and delivery through MSC-Exos (*230*).

Subsequently, various other drug delivery platforms were developed based on the MSC-Exos design. One study treated PDAC in a mouse tumor xenograft model with BM-MSC-Exos enriched with paclitaxel and gemcitabine monophosphate (GEMP), which resulted in increased overall survival (*231*). This novel exosome drug delivery system demonstrated high selectivity for PDAC cells and effective penetration of tumors (*231*). Research is also underway to explore dual-delivery biological systems using MSC-Exos, lectin 9 siRNA loaded *via* electroporation, and surface modification with

oxaliplatin. These approaches enhance the accumulation of chemotherapeutic agents within pancreatic tumors while reducing their systemic distribution (*232*). Exosomes produced by these novel MSC-Exos systems are both modified with targeted ligands and genetically engineered to retain their original characteristics, and hold great promise for efficient chemotherapy drug delivery to tumor cells with significantly enhanced tumor targeting.

4.8. Brain cancer

In a comprehensive review, Ordóñez-Rubiano *et al*. (*233*) noted that exosomal miRNAs play a significant role in the progression of glioblastomas, as they are released during disease progression, and contribute to tumor growth and invasion. Exosomal miRNAs, such as miR-21, miR-301, and miR-301a, are transferred to the surrounding cells, wherein they disrupt homeostasis in normal cells and enhance the proliferation and invasion of malignant cells. Compared to exosomes from normal brain tissue, tumor cell-derived exosomes exhibited significantly elevated levels of miRNAs, including miR-222, miR-9, and miR-26a, which activate various signal transduction pathways that stimulate tumor growth. Notable exosomal miRNAs involved in glioblastoma progression include miR-301a, miR-151a, miR-21, miR-1246, miR-29a, miR-92a, miR-9, miR-26a, and miR-375. These miRNAs represent potential biomarkers and therapeutic targets in glioblastoma.

MSC-Exos have been shown to effectively regulate immune responses and promote the repair and regeneration of damaged neurons. Through the ability to traverse the blood-brain barrier, MSC and their exosomes can be used as carriers for effector molecules in therapeutic applications for brain cancer treatments (*234*). Using flow cytometry and *in situ* hybridization, researchers have demonstrated that MSC-secreted exosomes localized to co-cultured glioma cells, delivering exosomal miR-145 and miR-124, which decreased glioma cell migration and self-renewal by reducing *synaptonemal complex protein 1* (*SCP-1*) and *SRY-box transcription factor 2* (*Sox2*) gene expression (*235*). Additional experiments in a mouse glioma xenograft model showed that intracranially administered MSC secreted exosomes transferred a fluorescent-labelled miR-124 mimic to tumor cells *in vivo* (*235*). The transfection of MSCs with extracellular vesicles containing miR-146b and subsequent injection of them into tumors has been shown to reduce the motility and invasiveness of glioblastoma cells in a rat model (*236*). In a similar study, MSC-Exos carrying miR-133b were shown to reduce EZH2 expression and downregulate the Wnt/β-catenin pathway in co-cultured U87, U251, LN229, and A172 human glioma cells, which inhibited cell proliferation, migration, and invasion (*237*).

The treatment of glioblastoma tumors with radiation and chemotherapy often results in the development of resistance to these therapies. The limitations of current treatments are in large part due to the inability of clinicians to precisely deliver therapeutic drugs to the glioblastoma multiforme (GBM) tumor site. To overcome this difficulty, researchers are investigating the use of MSC-Exos for efficient effector molecular delivery. Munoz *et al*. (*238*) reported that expression of miR-9 in temozolomide-resistant GBM cells was greater than that in healthy cells, and that non-resistant cells were transformed to resistant cells by the intercellular transfer of miR-9 *via* GBM-derived exosomes. They used BM-MSCs engineered to secrete exosomes carrying an anti-miR-9 molecule to silence the expression of miR-9 in co-cultured temozolomide-resistant GBM cells, which led to temozolomide sensitization and increased cell death accompanied by increased caspase activity (*238*).

5. MSC exosomes in clinical applications

The ability to sterilize exosomes by filtration and their lower immunogenicity (*104*) results in lower risks of adverse effects compared with MSC transplantation (*21*). The lack of replication and differentiation result in more predictable biological responses and shorter half-life compared with transplanted MSCs (*239*), and the small size and lipophilic membrane of exosomes can contribute to greater penetrance of physiological barriers (*240*). The over-expression of CD47 in exosomes produced by human BM-MSCs and AT-MSCs allows evasion of immune cell phagocytosis, which ensures the bioavailability of MSC-derived exosomes at the tumor site (*241*). The ability to load MSC-Exos with therapeutic molecules allows delivery of a wide range of biologically active cargo (*242*).

Exosomes are preferentially internalized by recipient cells of the same cell-type as the secreting host cell due to the conservation of cell membrane protein signatures (*243*). Cell signature based targeting also occurs with exosomes produced by cancer cells (*244*), with exosomes targeting both malignant and non-malignant cells of similar origin (*245*). Thus, the parent cell can be selected to ensure the sorting of target-cell ligands into exosomes to mediate delivery to specific target cell types (*243*). MSC-Exos also demonstrate cell signature targeting specificity, and have shown substantial potential for targeting tumor cells for anti-cancer drug delivery, enhancing efficacy under low toxicity conditions (*246*).

5.1. Potential tumor-related effects of MSC-Exos

Studies have shown that MSC-based treatments can modulate both tumorigenic and tumor-suppressive processes (*247*), and that MSC-Exo transplantation can suppress the growth and progression of histologically different types of cancer (*132,248*). However, tumor-derived exosomes have been shown to contribute to

tumor progression (*249*) and resistance to chemotherapy (*250*), and similar studies found that MSC-Exos also contributed to resistance (*151*), angiogenesis (*251*), cell proliferation (*252*), and migration (*253*). By contrast, other studies concluded that MSC-Exos inhibited the development of resistance (*254*), increased chemosensitivity (*255*), inhibited angiogenesis (*143*) and tumor cell proliferation (*256*), and promoted tumor cell apoptosis (*257*). Due to these conflicting findings, the tumorigenic potential of transplanted MSC-Exos remains a safety concern for the development of anti-cancer therapies (*258*).

5.2. Safety of MSC-Exo anti-cancer therapeutics in clinical trials

Most clinical trials investigating exosomes in cancer patients have focused on the analysis of plasma exosomes as diagnostic or companion diagnostic biomarkers (*259*). Investigations of MSC-Exos for anti-cancer therapies are few in number. Phase 1 clinical trials have been performed to investigate the safety of various MSC-Exos transplantation protocols. Using our search and exclusion criteria, we identified nine registered trials investigating applications of MSC-Exos for cancer treatments (Table 1). Only one of these trials, NCT03608631 (n = 9), uses MSC-Exos in anti-cancer therapy for a solid tumor malignancy. In NCT03608631, patients with metastatic pancreatic cancer are treated with exosomes derived from hBM-MSCs containing siRNA that silence the expression of $Kras^{G12D}$, which is a primary driver of tumor progression in PDAC (*260,261*).

The results of NCT03608631 have not yet been published, but the preprint report of the phase 1b clinical data was recently made available (*262*). The NCT03608631 investigators reported no adverse reactions or toxicity despite using a dosing regimen designed to determine the highest tolerable dosage. Analysis of post-treatment tumor tissue samples showed that Ras signaling was downregulated by suppression of ERK phosphorylation, the number of $PanCK^+$ cancer cells were reduced, and the numbers of $aSMA^+$ stromal cells were increased or remained stable compared to the results of the pretreatment analysis. Further post-treatment analysis of tissue samples showed increases in intratumoral $CD8^+$ T cells, $CD4^+$ $Foxp3^+$ Tregs, and $CD4^+$ $Foxp3^-$ cells compared to the pre-treatment analysis, suggesting that a favorable anti-tumor immune response was induced within the TM. Six patients experienced disease progression after three treatment cycles. One patient experienced disease progression after five treatment cycles. One patient experienced disease progression after six treatment cycles, and one patient experienced disease progression at 3 months following six treatment cycles (*262*). Though the efficacy findings of NCT03608631 are mixed, the safety data are an important contribution to the overall body of research in this field.

With regard to evaluating the safety of MSC-Exos for anti-cancer treatments, caution must be exercised in comparisons of safety data from studies investigating the application of MSC-Exos for pathologies other than cancer, due to the need to evaluate the potential tumorigenic properties of MSC-Exo therapeutics. One of other trials identified, NCT06245746, is investigating the use of MSC-Exos in an intervention for acute myeloid leukemia (Table 1). However, this study is still in the recruiting stage. Six of the remaining trials are also in the recruiting or pre-recruiting stages. The last remaining phase 1 trial, NCT04134676, has been completed (Table 1). However, this study administered MSC-Exos in a topical treatment for wound healing, thereby limiting the suitability of its safety data for comparison with those of solid tumor studies, which most often administer anti-tumor therapeutics intravenously (IV) or intratumorally (IT). In the NCT03608631 and NCT06245746 trials, the MSC-Exos were administered by IV infusion.

With so few studies of MSC-Exos for anti-cancer treatments available for analysis, we considered comparisons with studies using non-MSC derived exosomes for the evaluation of adverse effects related to administration route and toxicity. A recent systematic review identified 10 clinical trials investigating the use of exosomes for anti-cancer treatments (*259*). Among these were NCT01159288, NCT05375604, NCT04592484, and NCT05559177 (Table 1), which investigated non-MSC derived exosome treatments for solid tumor cancers. The NCT01159288 trial, which was completed in 2015, used exosomes derived from IFN-γ-maturated DCs to treat non-small-cell lung cancer (NSCLC) (*263*). The NCT05375604 trial used human embryonic kidney cell (HEK293) derived exosomes (HEK-Exos) containing anti-sense oligonucleotides that inhibit expression of the *signal transducer and activator of transcription 6* (*STAT6*) gene (*264*) for the treatment of patients with advanced hepatocellular carcinoma and those with gastric cancer or colorectal cancer with liver metastases.

The NCT04592484 trial also used HEK-Exos that were loaded with exogenous cyclic dinucleotide (CDN) agonists of the stimulator of interferon genes (STING) pathway (*265*) for the treatment of solid tumors, including cutaneous squamous cell carcinoma, head and neck squamous cell cancer, anaplastic thyroid carcinoma, and triple negative breast cancer. The NCT05559177 trial used chimeric exosomes in patients with recurrent or metastatic bladder cancer. These exosomes were derived from cells produced by the fusion of nuclei of bladder cancer cells with peripheral blood antigen presenting cells, with both types of cells obtained from each patient to produce a personalized cancer vaccine.

Of these four additional clinical trials using non-MSC derived exosomes, safety data are available for NCT01159288 only. Of the seven patients included in

Table 1. Summary of clinical trials investigating various exosome-based therapies

Patient criteria (sample size)	Study phase (status)	Intervention summary (route)	Clinical safety results	Trial registration (*Ref.*)
Metastatic pancreatic cancer (n = 9)	Phase 1b (ongoing, not recruiting)	hBM-MSCs carrying siRNA to silence $Kras^{G12D}$ expression (IV)	No adverse reactions or toxicity	NCT03608631 (*262*)
Acute myeloid leukemia (n = 9)	Phase 1 (recruiting)	hUC-MSC-Exos (IV).	Not available	NCT06245746
Rectal cancer (n = 20)	Phase 1 (not yet recruiting)	Human placenta-derived MSC-Exos to prevent early anastomosis leakage	Not available	NCT06536712
Multiple organ failure (n = 120)	Phase 1 (not yet recruiting)	MSC-Exos (IV)	Not available	NCT04356300
Pilonidal sinus/pilonidal disease (n = 120)	Phase 1 (recruiting)	Drug+/-MSC+/-MSC-Exos (site injection)	Not available	NCT06391307
Dystrophic epidermolysis bullosa (n = 10)	Phase 1 (recruiting)	Allogeneic MSC-Exos (topical)	Not available	NCT04173650
Amyotrophic lateral sclerosis (n = 38)	Phase 1 (recruiting)	hUC-MSC-Exos (nasal drop)	Not available	NCT06598202
Patients undergoing hematopoietic stem cell transplantation (n = 120)	Phase 1 (recruiting)	MSC-Exos (topical oral and bladder irrigation)	Not available	NCT06599346
Chronic ulcer (n = 38)	Phase 1 (completed)	Wharton jelly-MSC-Exos (topical)	No safety data	NCT04134676 (*272*)
Advanced NSCLC (n = 41)	Phase 2 (completed)	IFN-γ-maturated DC-Exos (intradermal) after oral cyclophosphamide	Grade-3 hepatotoxicity (n = 1)	NCT01159288 (*263*)
Advanced HCC, gastric cancer, colorectal cancer (n = 9)	Phase 2 (terminated)	HEK-Exos containing siRNA to silence STAT6	Not available	NCT05375604 (no publication)
Advanced solid tumors (n = 27)	Phase 2 (completed)	HEK-Exos loaded with CDN agonists of STING	Not available	NCT04592484 (no publication)
Recurrent or metastatic bladder cancer (n = 9)	Phase 1 (unknown)	Personalized chimeric exosome cancer vaccine (not reported)	Not available	NCT05559177 (no publication)
Advanced NSCLC (n = 9)	Phase 1 (completed)	DC-Exos (intradermal)	10 events, grade-1,2	Not registered (*266*)
Metastatic melanoma (n = 15)	Phase 1 (completed)	DC-Exos (intradermal)	None ≥ grade 2	Not registered (*273*)
Advanced colorectal cancer (n = 40)	Phase I (completed)	Autologous exosomes from patient ascites (intradermal)	42 events, grade-1,2	Not registered (*268*)

NCT01159288, one experienced grade-3 hepatotoxicity with no other adverse events reported (*263*). Through our screening of review articles retrieved in our literature search, we identified three additional trials that were not registered with *clinicaltrials.gov* (Table 1). These studies used intravenous infusions of DC-derived exosomes to treat advanced NSCLC (*266*), metastatic melanoma (*267*), and advanced colorectal cancer (*268*), with all reporting that the various treatments were well tolerated (*269*).

The sum of these results for non-MSC derived exosomses and MSC-Exos based treatments for solid tumors suggest that the risk of adverse effects associated with intravenous infusions of exosome therapeutics is low. However, more safety data are needed. The addition of healthy control arms in future studies might provide important information regarding possible adverse effects related to administration routes and dosing regimens. Moreover, the sample sizes of most of these clinical trials are quite small. Future multicenter studies and international collaborations could increase the number of patients participating in the development of these urgently needed improvements in treatments for solid tumor malignancies. Improved reporting of safety data and updating of online registry entries would benefit investigators planning new studies. The NCT03608631 investigators proposed continuing the trial with a combination therapy using the $Kras^{G12D}$-suppressing exosomes and an unspecified inhibitor of immune checkpoint CTLA-4 (*270*), a known driver of immunosuppression in pancreatic cancer (*271*). This approach is supported in part by the results of *in vitro* and animal experiments (*262*). We look forward to the publication of their future clinical findings.

6. Conclusions

Through our search of the available literature describing the therapeutic potential of MSC-Exos for the treatment of solid malignancies, we found that preclinical and phase-1 clinical studies provide exciting evidence regarding the safety and potential efficacy of MSC-Exos in the treatment of various solid tumors, including breast, lung, gastrointestinal, pancreatic, colorectal, brain, and urological cancers. These findings suggest that MSC-Exos based therapies have the potential to revolutionize cancer treatment. However, we also recognized that MSC-Exos possess certain dual characteristics by which their properties have been observed to promote tumor progression, while also being observed to suppress it under other conditions. This complexity may be related to the origin of MSC exosomes, the types of molecules they carry, and specific conditions within the TM. Such conflicting properties need not diminish their potential as therapeutic tools. The selective loading of MSC-Exos with tumor-suppressive miRNAs or anti-cancer drugs achieved thus far represents great potential for the development of an effective delivery system for precisely targeting cancer cells. Ultimately, genetic engineering of the contents of exosomes will likely be required to favor the expression of anti-tumor molecules and suppress those linked to tumorigenic processes. Future research should focus on elucidating the mechanisms of MSC-Exos and their functions in different TMs, as well as exploring how to optimize the composition of MSC-Exos to enhance their therapeutic efficacy to further lay the groundwork for novel clinical applications.

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