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Review

Exosome-based miRNA delivery: Transforming cancer treatment with mesenchymal stem cells

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ABSTRACT

Recently, increasing interest has been in utilizing mesenchymal stem cell-derived extracellular vesicles (MSC-EVs), especially exosomes, as nanocarriers for miRNA delivery in cancer treatment. Due to such characteristics, nanocarriers are specific: biocompatible, low immunogenicity, and capable of spontaneous tumor accumulation. MSC-EVs were loaded with therapeutic miRNAs and minimized their susceptibility to degradation by protecting the miRNA from accessibility to degrading enzymes and providing targeted delivery of the miRNAs to the tumor cells to modulate oncogenic pathways. In vitro and in vivo experiments suggest that MSC-EVs loaded with miRNAs may inhibit tumor growth, prevent metastasis, and increase the effectiveness of chemotherapy and radiotherapy. However, these improvements present difficulties such as isolation, scalability, and stability of delivered miRNA during storage.

Furthermore, the issues related to off-target effects, as well as immunogenicity, can be a focus. The mechanisms of miRNA loading into MSC-EVs, as well as their targeting efficiency and therapeutic potential, can be outlined in this manuscript. For the final part of the manuscript, the current advances in MSC-EV engineering and potential strategies for clinical application have been described. The findings of MSC-EVs imply that they present MSC-EVs as a second-generation tool for precise oncology.

Contents

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1. Introduction

Cancer has always been a significant problem for the entire world, with millions of new diagnoses every year [1]. Although considerable progress has been achieved in cancer treatments, such as surgeries, chemotherapies, and radiation, these methods usually possess prominent disadvantages [2]. Their drawbacks generally lack specific targeting, severe side effects, and a chance of developing resistance [3]. Therefore, there is a persistent need for more distinct and anticipated treatment methods. One of the pervasive complications of any cancer therapy is the inability to attack the cancer cells [6] selectively. To be more precise, the deficiency of specificity while attacking the component usually results in systemic toxicity and numerous adverse side effects, which considerably impair the patient's quality of life [4,5]. In addition to this, cancer cells are capable of developing resistance, making therapies substantially less efficient over time [6]. It is also justified to mention that the tumors present substantial diversity, and the TME is complex [7]. All these facts contribute to the overall ambiguity of treatment effectiveness [8]. As an alternative to similar methods, targeted treatment aims to attack solely the cancer cells. It targets the molecules that protect these cells from dying and helps destroy them more effectively. Owing to its targeted character, the treatment is supposed to do less damage to healthy tissues. Attention to different molecular targets may provide additional opportunities for more specific and stronger cancer treatments.

MSCs are multipotent stem cells in various tissues, including bone marrow, fatty tissue, and umbilical cord blood [9]. These cells may develop into multiple cell sorts, provided they are correctly managed, such as osteoblasts, chondrocytes, and adipocytes [10]. These unique characteristics and their impact on the immune system have made MSCs a crucial tool in regenerative medicine and cancer therapy [11]. MSCs are mainly identified by their origination from bone marrow, but they may also be obtained from adipose tissue, umbilical cord blood, and other sources. MSCs recognize the restriction on a plastic culture and their distinctive expression of surface markers like CD73, CD90, and CD by their distinction from different types of cells [12]. Possibly differentiating into mesenchymal lineages is a further distinction [13]. MSC isolation cultivation in vitro is simple and facile, and their slight immunogenic response makes them ideal for clinical utilization [14]. The most typical therapeutic use of MSCs is to refresh tissues, but they also have a great cancer therapy. When injected, MSCs can trace the tumors that occurred and, in most situations, have a holistic anti-tumor action [15]. Furthermore, MSCs can be modified to transport therapeutic compounds directly to tumors, thereby improving treatment effectiveness while minimizing overall toxicity [16].

EV are particles the cell releases into space and enclosed by a membrane. They are about cell communication, as they carry proteins, lipids, and nucleic acids, which can influence the cells to which they deliver their content [17]. Their subgroups are exosomes, microvesicles or ectosomes, and apoptotic bodies [18]. According to their size, formation, and content, they consist of exosomes or cultured supernatants, excentric materials, microvesicles, matrix vesicles as well as prostasomes secreted by the prostate gland, and electron-dense lysosomes emitted as a result of programmed cell death [19]. The size of exosomes can range from 30 to 150 nm; the endosomal system forms them. Microsomes are bigger, from 100 to 1000 nm, and form by budding off the plasma membranes [20]. The biggest one, the apoptotic body, is 500–2000 nm in diameter and is created due to programmed cell death [21]. Their size is only one of the properties of extracellular vesicles; their content characterizes them better [22]. EVs actively participate in many physiological processes, such as transferring bioactive molecules from one cell to another. They promote an immune response for angiogenesis, tissue repair, and other methods [23]. They help in cell-to-cell communication, exchanging actionable molecules like proteins, lipids, and RNAs. Delivering their content via biofluids changes the physiological state of the receiving cell [24]. EVs knowingly or unknowingly influence cells' movement, growth, and differentiation. Transferring oncogenic materials and adjusting the tumor microenvironment help the tumor's advancement, spread, and resistance to treatment.

MiRNAs are a sub-class of small, ncRNA molecules that modulate the function of genes after their transcription [5,25]. Typically, they attach to opposite segments in target RNAs, catalyzing either the corresponding mRNA's breakup or the translation repression [26]. This action method remains one of the foundations for maintaining normal cell homeostasis, yet cancerous conditions can potentially disrupt this process [27]. In terms of mechanisms,

miRNAs can bind to the 3′ UTR of their target mRNAs, leading to one of the two said RNA outcomes. This gene expression adjustment is utilized across various cell behaviors related to growth, programmed cell death, and differentiation [28,29]. More specifically, the irregular expression of miRNAs moderates the risk of cancer by either overexpressing or reducing the presence of genes responsible for tumor formation [30], with the incidence of controlling miRNAs in a vast majority of cancers, explicitly using miRNAs identified as either oncogenes or tumor suppressors, unusual concentration levels of miRNAs in given cells can lead to uncontrolled proliferation. At the same time, they make them contumacious to apoptosis and increase the cell's metabolism [31,32]. Restoring normal miRNA levels in cancer cells ensures another opportunity for treatment, suggesting that miRNAs can play a pivotal part in the procedure. While synthetic nanoparticles, liposomes, and viral vectors have demonstrated significant promise in delivering therapeutic agents, they often face challenges such as high immunogenicity, limited biocompatibility, and difficulties overcoming biological barriers [33]. In contrast, MSC-derived extracellular vesicles (MSC-EVs) exhibit low immunogenicity, natural biocompatibility, and an intrinsic ability to target tumor microenvironments, making them a compelling alternative for miRNA delivery in cancer therapy [34]. This review examines the prospects of utilizing MSC-derived EVs to deliver miRNAs to improve targeted cancer therapies, focusing on overcoming current challenges, enhancing effectiveness, and presenting a novel strategy for cancer treatment.

2. Methodology

A comprehensive literature search was conducted using PubMed, Scopus, Web of Science, and Google Scholar with keywords like "Mesenchymal Stem Cell-Derived Extracellular Vesicles," "miRNA delivery," and "cancer therapy." Inclusion criteria were peer-reviewed articles from 2000 to 2023 focusing on MSC-EVs for miRNA delivery in cancer therapy, while exclusion criteria involved non-peer-reviewed sources and irrelevant studies. Results were critically appraised to highlight strengths, limitations, and research gaps and make recommendations for future research.

3. Mesenchymal stem cell-derived extracellular vesicles (Msc-Evs)

3.1. Characteristics of MSC-EVs

3.1.1. Isolation and characterization methods

MSC-EVS are isolated to ensure they are pure, intact, and functional [35]. There are numerous methods, each with advantages and disadvantages [36]. One of the most frequently used methods is differential centrifugation [37]. The technique implies several stages, such as low-speed centrifugation to discard cells and large debris, medium-speed centrifugation to remove larger vesicles and apoptotic bodies, and high-speed centrifugation, or ultracentrifugation, to pellet the MSC-EVs [38]. The technique works and is used rather frequently, but it is time-consuming and probably cannot separate them from all possible contaminants [39]. As for density gradient centrifugation, it is based on the separation of vesicles by their buoyant density. It is possible to use a density gradient medium, such as sucrose or iodixanol [40]. Later, the MSC-EVs are extracted from the fractions of equal density. The method is more efficient regarding contaminant separation and is more laborious as it requires special equipment [41].

Size-exclusion chromatography is used to separate MSC-EVs. In this method, vesicles are fractionated as they pass through a column filled with porous beads based on size. Thus, smaller MSC-EVs will be eluted first, whereas the bigger vesicles will be retained longer [42]. One of the advantages of SEC is that it uses mild conditions, allowing the vesicles to keep their integrity and functionality [43]. However, it may be less efficient in removing protein contaminants such as those from bovine foetal serum. To ensure that the isolated MSC-EVs are what they are supposed to be and to gauge their quality, they must be characterized [44]. The most commonly used methods to measure the size of MSC-EVs and their concentration are nanoparticle tracking analysis and DLS, which can also study zeta potential [45]. Morphology of vesicles may be viewed with the help of TEM. The flow cytometry permits analysis of MSC-EV-specific surface markers [46]. Finally, western blotting may identify specific EV-associated proteins, including CD63, CD81, and TSG-101, as markers for MSC-EVs [47].

3.1.2. Biochemical composition

Biochemical composition of MSC-EVs points to their origin and role in intercellular signaling. For this reason, these EVs possess a lipid double layer enclosing many bioactive compounds, such as proteins, lipids, and nucleic acids [48]. As for proteins, MSC-EVs contain tetraspanins, HSP, and cytoskeletal proteins, which are relevant for constructing, supporting, and functioning EVs [49]. In addition, these vesicles include several enzymes, growth factors, and cytokines, enhancing their therapeutic effects [50]. For instance, TGF-β and IGF-1 contained in MSC-EVs trigger tissue healing and regulate the immune response. The lipid component of MSC-EVs is also important, as the extracts are rich in cholesterol, sphingomyelin, and phosphatidylserine. These lipids preserve the integrity of EVs and facilitate their behavior toward the target cell [51]. Lipids are central to the vessel circulation of MSC-EVs in blood, thus increasing their effectiveness as a therapeutic agent [52]. As for nucleic acids, their presence in MSC-EVs, particularly miRNAs, is essential. These small ncRNAs are responsible for gene regulation after transcription and participate in the most important biology processes: cell growth, differentiation, and apoptosis [53]. Since the profile of miRNAs in MSC-EVs is contingent upon the condition of the donor MSCs and impacts the recipient cell, these vesicles acquire a novel purpose as a source of miRNAs for treatment [54].

3.2. Mechanism of mirna loading into MSC-EVs

3.2.1. Techniques for miRNA encapsulation

One crucial process, the efficacy of which determines the therapeutic properties of EV derived by MSCs, is the incorporation of miRNAs [55]. Over the past several years, several techniques have been developed to enhance the productivity of loading and stability of miRNAs in MSC-EVs [56]. According to Li et al. electroporation is frequently employed when temporary openings in the vesicle are generated through an electric field, thus allowing miRNAs to pass. While overwhelmingly effective at ensuring high miRNA loading, this technique can irreversibly compromise the structural integrity of the EVs if not correctly managed. Moreover, several approaches exist based on inserting transfection reagents and, thus, miRNAs into vesicles [57].

A method of culturing mesenchymal stem cells, co-incubation, is employed. In this case, synthetic miRNAs are also maintained in the culture medium [58]. This simple approach allows miRNAs to be taken into vesicles formed by MSCs as they are released into the medium [59]. However, the loading efficiency with this approach is typically lower than electroporation or chemical transfection, with the added phosphorylation step for synthetic miRNAs during chemical transfection affecting the overall loading capability [60]. One of the advantages of co-incubation is that loading is carried out in parallel with the culture of mesenchymal stem cells, which

supports the maintenance of the integrity and function of both the vesicle and miRNA biological structures [61].

3.2.2. Efficiency and stability of miRNA loading

Using miRNA-loaded vesicles in MSC-EV-based therapies is only effective if the vesicles can be reliably loaded with the necessary RNA [62]. Electroporation and chemical transfection generally result in higher loading efficiencies than co-incubation [63]. However, further research is needed to refine these techniques, improving the balance between loading and the vesicles' integrity [64]. This will require optimizing factors such as miRNA concentration, the strength of the electric field during electroporation, and the type of transfection agents used [65]. Other considerations include the stability of miRNAs within MSC-EVs [66]. The vesicles and accompanying bound proteins create an environment that protects the miRNAs during long-term storage, transportation, and even delivery to the cancer cells [67]. The latter is particularly stressed due to the vapor pressure reagents, exposing the miRNAs to the breakdown by the cellular enzymes.

In contrast, the lipid bilayer helps protect the miRNA from stress and the environment, ensuring their availability in the cells [68]. There are also advanced solutions to this issue, such as modifying the MSC-EV surface with targeting ligands that will increase the efficiency of vesicle internalization, in contrast with the mechanisms described earlier [69]. These options would increase the specificity of the EVs while preserving most of their stability, improving the safety of the MSC-EVs in the context of their potential use in therapies and, therefore, the effectiveness of the delivered miRNA [70].

4. Therapeutic potential of MSC-EV-mediated Mirna delivery in cancer

4.1. Mechanisms of MSC-EVs targeting cancer cells

The mechanisms of action through which MSC-derived extracellular vesicles target cancer are linked to several essential molecules. These vesicles have integrins, tetraspanins, and other surfaces [71]. First, the interaction of integrins carried by MSC-EVs with a component of the extracellular matrix is activated, given the expression of fibronectin and vitronectin [72]. Specifically, αvβ3 and αvβ6 carried by MSC-EVs link to the extracellular matrix at the site of the cancer [73]. The chemokine gradient plays another role in localizing MSC-EVs in the tumor. The presence of CXCL12 in higher levels of cancer allows these vesicles to migrate to the required site, and the CXCR4 receptor on MSC-EVs is overexpressed to facilitate this interaction [74].

Furthermore, the CD44 receptor on MSC-EVs interacts with hyaluronic acid in the tumor environment [75]. This link assists in the retention of vesicles in the cancer site and helps with the internalization of MSC-EVs in cancer cells, stimulating the delivery of therapeutic miRNAs [76]. MSC-EVs can also be engineered to carry material that increases their target on the neoplasm [77]. For example, including the EGFR ligand in MSC-EVs elevates their concentration in the tumor that overexpresses such ligands in breast and lung cancer cases. Importantly, this modality reduces the uncontemplated actions of vesicles on other cells around the cancer [78].

MSC-EVs offer several advantages in delivering therapeutic miRNAs for cancer treatment [79]. First, they are compatible with biological systems and have a low ability to induce immune responses. This would make the EVs ideal for repeated use without causing many immunity issues. Moreover, as the EVs can be obtained as isografted from the same patient or allografted from a donor, the chances of a significant negative immune response are minimized [80]. As for the mechanism, MSC-EVs protect the miRNAs they carry from destruction by the enzymes in the bloodstream, thus improving their availability and stability. This is achieved through the lipid bilayer that envelops EVs, which would protect miRNAs from being broken down by ribonucleases, a portion of enzymes found outside cells [81]. Overall, using MSC-EVs to deliver therapeutic miRNAs would increase the number of functional miRNAs reaching the target cancer cells.

Second, the EVs can naturally target, meaning the miRNAs can be delivered directly to the tumor site [82]. This ability reduces off-target effects, thus lowering systemic toxicity and allowing for lower therapeutic doses. Looking at the mechanism, MSC-EVs contain miRNA-modifying proteins, which would allow for the miRNAs to escape the multicast-mediated suppression of cell function [83]. The cluster of miRNAs introduced into MSC-EVs would then be transferred to the target cells [84]. In addition, as MSC-EVs can be modified to display specific surface receptors, they can be used to target specific sites of interest, such as the cancer cells that have already been identified [85].

Moreover, as with other types of EVs, MSC-EVs can pass the natural barriers in a biological system, such as the blood-brain barrier [86]. They can then treat tumors in previously inaccessible regions with therapeutic miRNAs [87]. This would extend the list of tumors that might be able to be impacted using MSC-EV-based miRNA delivery to include practically any type (Fig. 1). Compared to synthetic nanoparticles and liposomes, MSC-EVs offer distinct advantages due to their biological origin, which allows them to evade immune detection and target tumor cells naturally [88]. While liposomes require functionalization with targeting ligands, MSC-EVs inherently express surface proteins, such as integrins and tetraspanins, which facilitate tumor-specific delivery [89]. Additionally, despite their high transfection efficiency, viral vectors pose risks of insertional mutagenesis and immunogenicity, challenges not encountered with MSC-EVs [90]. These attributes position MSC-EVs as a safer and potentially more effective platform for miRNA delivery.

4.2. Therapeutic efficacy of MSC-EV-mediated miRNA delivery in cancer therapy

4.2.1. Preclinical studies and experimental models

Over the years, many preclinical studies and experimental models have shown that EVs derived from MSC are an efficient

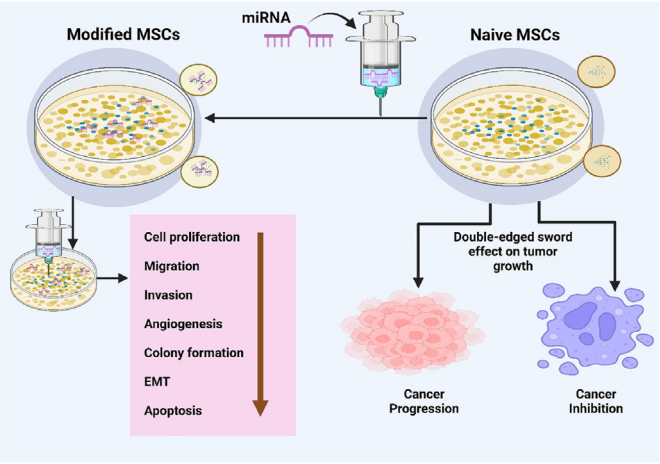

Fig. 1. Shows the effects of miRNA-modified MSCs versus naive MSCs on cancer. Modified MSCs, loaded with miRNA, inhibit cell proliferation, migration, invasion, angiogenesis, and EMT and promote apoptosis, while naive MSCs have a dual impact on tumor growth.

delivery vehicle for miRNAs in cancer therapy, where each of them provided insight into this desirable therapeutic approach to some extent. For example, Lee et al. demonstrated that miR221-3p-containing exosomes from hBMSCs suppressed angiogenesis and tumor growth in vitro and in vivo. We further identified miR-16 as a mediator of the suppression of expression levels of VEGF in breast cancer cells [91]. Based on this pioneering study, continuing these investigations into the potential of MSC-derived exosome miRNAs in reprogramming tumor microenvironments could be interesting. Expanding upon this basis, Pakravan et al. showed that miR-100 was one of the highly expressed exosomal microRNA derived from hBMSCs.

Further, they indicated the ability to suppress angiogenesis in vitro via reduced levels of VEGF in breast cancer cells [92]. In addition, their results provided some more clearance about the mechanism by which miRNA-loaded exosomes influence tumor progress since mTOR/HIF-1α signal ways [93]. Such results underscore MSC-derived EVs' impact in regulating vital signaling pathways that govern tumor cell proliferation and invasion. Additionally, insights into these findings are found in work by Ono et al. which showed that the BM2 cells of breast cancer acquired dormancy properties attributed to decreased growth and invasion when cultured with EVs-MSC [94]. The researchers found that MSC EVs contained relatively more miR-23b than fibroblast-derived EVs. Overexpression of miR-23b in BM2 cells induced dormancy by negatively targeting MARCKS, an important effector in cell cycling and motility [95]. These results indicate the possibility of MSC-EVs to establish dormant cancer cells, which is important in controlling various cancers associated with metastasis.

Shimbo et al. further confirmed this theory because hBMSCs enriched with miR-143 could inhibit the invasion and proliferation of osteosarcoma cells. The study highlighted the multi-cancer targeting capability of MSC-EVs that is mediated through miRNA. Another therapeutic miRNA of MSC-EVs is mir-34a-5p, which suppresses cell growth and induces apoptosis in CRC cells via decreasing expression levels of the c-MYC/DNMT3a/PTEN signaling pathway, including genes that promote survival pathways [96]. Similarly, Korpal et al. showed that MSC-EVs containing miR-200c, which resulted in the inhibition of EMT (a crucial stage during cancer metastasis), were able to down-regulate transcription factors such as ZEB1 and ZEB2 [97] By modulating these pathways, MSC-EVs loaded with miRNAs can effectively suppress tumor growth and prevent the spread of cancer to distant organs.

Studies in the context of different cancers, especially those done on brain and lung tumor models, have established that miRNA-loaded MSC-derived EVs can reach their target site to show a therapeutic perspective [98]. Katakowski et al. transfected rat bone marrow-derived MSCs with plasmids that encode miR-146b to produce exosomes overexpressing this particular molecule. Co-culture of these exosomes with 9 L cells results in a substantial decrease in growth rate for the glioma cell line. In addition, the exosomes were able to dramatically decrease glioma xenograft growth via direct intratumoral injections into rat brain tumors, thereby suggesting a strong potential for miR-146b in promoting anti-tumor efficacy against this aggressive disease [99]. Similarly, Kim et al. found that exosomes enriched with miRNA-584-5P from human MSCs could suppress the proliferation and migration of U87 glioma cells and induce apoptosis. Its anti-inflammatory effect targeted Cytochrome P450 2J2 (CYP2J2) and inhibited the Akt or MAPK pathway [100].

Consistently, numerous additional studies have further supported MSC-EVs in treating glioma. For example, human MSC-exosomes with miR-375 over-expression could decrease SLC31A1 manifestation in U87 glioma cells. This inhibition attenuated cell proliferation, migration, and invasion and increased apoptosis. In vivo studies using murine xenografted human neuroblastoma tumors in nude mice demonstrated that these exosomes were effective at reducing tumor growth (Fig. 2) [101] Yan et al. miR-512 significantly downregulated JAG1 by miRNA and luciferase reporter analyses. After transfecting U87 glioma cells with CBSDMSC Exos containing miR-512 (BMSC-exo/CR), we observed inhibited cell proliferation, migration, and invasion of the BMSC-exo/CR group compared to the same amount of control-treated exosomal fractions from scrambled oligonucleotide-transfected donor mice. Thus, the inhibitory effects of miR-512-5p in most glioblastoma model mice indicate that exosomes with miR-512 expression could act as a new efficient strategy for treating gliomas and improving survival [102]. Results by Figueroa et al. further support the participation of miRNA exosomes isolated from MSCs in brain tumors. Exosomes derived from glioma-associated MSCs were operative in specifically driving the proliferation and tumorigenic ability of GLSCs. By miRNA profiling, a major mediator of these effects was the expression miRNA-1587, partly by inhibiting nuclear hormone receptor corepressor 1 [103]. Moreover, treatment of glioblastoma cells with MSCs overexpressing anti-miR-9 and co-cultured with temozolomide canceled the resistance phenotype. A flow cytometry study confirmed an enhancement in cell death associated with improved caspase activity during this reversal via direct stepwise transference of anti-miR-9 from exosomes to glioblastoma cells [104] (Fig. 2).

MSC-EV is not only for a brain tumor. Takahara et al. used further analysis and found that exosomes secreted from hAMSCs containing a high level of miRNA-145 exert inhibitive influence on the processes in prostate cancer development by enhancing apoptosis and activating Caspase-3/7 pathway [105] Furthermore, Liu et al. proven that hBMSC-derived EVs containing miRNA let-7i suppressed lung cancer cell growth through targeting the KDM3A/DCLK1/FXYD3 axis, also suggesting a broad spectrum of applications for MSC-derived vesicles as carriers of anti-cancer therapeutic molecules [106]. Although these results are promising, additional work is required to elucidate the roles of exosomal miRNAs and other uncharacterized cargoes in promoting cancer [107]. Therefore, this ongoing exploration is essential for realizing MSC-based EVs' therapeutic applications in oncology.

For instance, the advancement of focused ultrasound (FUS) technology has further elevated the course through which miRNAs are delivered in MSC-derived EVs [108]. Zhan et al. used FUS to

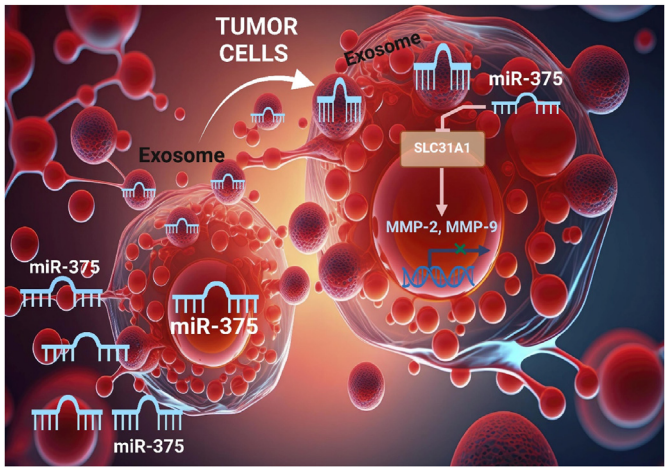

Fig. 2. Illustrates tumor cells releasing exosomes containing miR-375, which targets SLC31A1. This interaction downregulates MMP-2 and MMP-9 expression, potentially inhibiting tumor progression and metastasis by affecting the extracellular matrix and tumor microenvironment.

open the BBB temporarily and selectively, thereby creating a greater penetration of exosomes carrying the miR-1208 gene with anti-tumor activity. This enhanced the transportation of miR-1208 into glioma cells, including U251 and U373, where it significantly repressed METTL3 (a methyltransferase). The inhibition, in turn, reduced N6-methyladenosine (m6A) modification on the mRNA level of NUP214, decreased TGF-β signaling pathway activity, and suppressed tumor growth in vitro and vivo [109].

Although EVs derived from MSCs have demonstrated promising capacity in suppressing tumor growth, there is some evidence that these vesicles may even be involved in proliferative effects on cancer cells, leading to a dual role at the level of cancer progression. hBMSC exosomes, for example, were demonstrated to promote the proliferation and migration of multiple cancer types and tumorigenesis [110,111]. The miRNAs encapsulated within these EVs serve prominent roles in controlling these oncogenic mechanisms. One example, among many others, is miRNA-410 loaded into hUCMSC-derived EVs. By targeting the tumor suppressor PTEN, which negatively regulates cell proliferation and apoptosis, the functional study demonstrated that miR-410 promotes lung adenocarcinoma growth [112]. In parallel, miR-130b-3p was enriched in hUCMSC-EVs and exerted oncogenic functions by modulating the FOXO3/NFE2L2/TXNRD1 axis for facilitating lung cancer. This modulation results in higher tumor cell survival/proliferation, further supporting the oncogenic potential of MSC-EVs [113]. Hypoxia-conditioned hBMSC-derived EVs facilitate the delivery of miR-21-5p, which is upregulated. For example, this miRNA has been reported to inhibit apoptosis and induce the M2 polarization of macrophages in lung cancer cell proliferation and metastasis. These are associated with reduced protein levels from the antiapoptotic gene PDCD4, PTEN, and RECK. The data indicated that MSCs developmentally modulate their release pattern of EVs [114]. Moreover, lower content of miR-15a in exosomes derived from hBMSCs exposed to patients with multiple myeloma has also been shown as a crucial factor-induced tumor-related activity. The decrease of miR-15a in these patients indicates the loss of its tumor-suppressor activity, which will then promote malignancy [115].

Subsequently, research efforts have begun focusing on the active role of lncRNAs, mRNAs, and proteins in boosting several oncogenic processes via extracellular vesicles [116]. These EV-transported molecules have been described to affect tumor growth and metastasis in various cancer types [117]. Du et al. found that hUCMSC-EVs promoted renal cancer growth and metastasis via ERK1/2 and AKT signaling pathways. This latter HGF-producing phenomenon was strongly linked to a promoting effect on tumor growth, as the human input EVs triggered hepatocyte production of this protein [118]. Thus, the impact of mRNA-loaded EVs on tumorigenesis is further highlighted by this discovery [119].

Similarly, Zhao et al. revealed that the lncRNA PVT1 packaged by exosomes derived from hBMSCs promoted osteosarcoma cells to express an oncogenic protein, ERG. This occurred by rescuing the degradation and ubiquitination of ERG in combination with serving as a miR-183−5p molecular sponge. This led to a significant increase in tumor growth and metastasis, underlining the function of lncRNAs within EVs concerning cancer dissemination [120]. In another study, Mao et al. mBMSCs-derived exosomes were found to have higher levels of E3 ubiquitin-protein ligase UBR2. Extracellular vesicles secreted by metastatic gastric cancer cells have been used to treat cellular and animal models of these cancers, showing that UBR2 expression is upregulated by such exosomes, thereby promoting the growth and migration tumors through activation via the Wnt/β-catenin pathway [115]. This research further illustrates how the protein content within EVs can significantly impact cancer development [121].

EVs also influence the glioma microenvironment, as demonstrated by Qiu et al. who uncovered that CD44 from glioma-derived exosomes could trigger a miR-21/SP1/DNMT1 positive feedback loop within MSCs. The whole loop fostered the production of miR-21-abundant exosomes in glioma-associated MSCs (GA-MSC) and enhanced glioma progression via immune system suppression. Of note, the immunosuppressive effect of GA-MSC exosome containing miR-21 was stronger than that of glioma exosomes alone, highlighting a vital role for MSC in promoting an enhanced level of immune suppression within the tumor microenvironment [122]. Another study also showed that tumor cells, such as MSCs, could induce stromal cells to release miR-214-abundant-EVs through activating IL6/STAT3 signaling. In turn, tumor metastasis promotes the Introduction of that activation [123]. Altogether, these data indicate that diverse molecular cargoes of EVs, including miRNAs, lncRNAs, mRNAs, and proteins, are delivered to target cells with functional effects in cancer [124]. This detailed knowledge of the interactions is necessary for exploiting EVs as a new therapeutic ally in oncology and unveiling potential risks associated with tumorigenesis [125].

4.2.2. Synergistic effects with existing therapies

Consequently, the co-administration of MSC-EV-mediated miRNA delivery with conventional cancer therapies presents an appealing opportunity for generating synergistic responses and enhancing effective overall therapeutic outcomes [126]. Several papers have documented this approach's potential efficacy in various cancers [127]. For instance, Bai et al. showed that the miR-122 dramatically enhanced chemosensitivity on HCC cells and could be correctly loaded within exosomes secreted by adipose-derived mesenchymal stem cells (AMSCs). These exosomal interactors (in this case, miR-122) transferred from AMSCs to HCC cells are likely facilitating the treatment responsiveness of these adjacent cancerous hepatocytes by altering expression profiles in target genes using either a gain or loss-of-function mechanism based on our study concept [128]. In addition, Lou et al. determined that direct intra-tumoral injection of miR-122 loaded MSC-EVs increased the sensitivity of hepatocellular carcinoma cells to sorafenib by suppressing the expression of anti-apoptotic genes, anti-cancer to increase by way of reducing resistance against chemotherapy effect through, In addition, Lou et al. determined that direct intra-tumoral injection of miR-122 loaded MSC-EVs increased the sensitivity of hepatocellular carcinoma cells to sorafenib, by suppressing the expression of anti-apoptotic genes in addition anti-cancer to increase by way of reducing resistance against chemotherapy effect through introducing miRNA-loaded MSC-EVs [129].

Understanding MSC-EV in miRNA delivery well, some research has also tried to test the possibility of combining this gene therapy with radiotherapy [130]. Duan et al. the miR-34a-carrying MSC-EVs promoted the radiation sensitivity of A549 and H1299 cells via downregulating DNA repair genes. The strategy would complement radiotherapy and increase treatment efficacy at lower radiation doses without toxic side effects [131]. In liver diseases, similar synergistic effects have been observed [132]. Lou et al. demonstrated a stable packaging of miR-122 into exogenous MSC-derived EVs and translocation to the hepatoma cells. This transfer suppressed target genes, such as cyclin G1 and insulin-like growth factor 1 receptors within the cancer cells. In vivo, these MSC-EVs sensitized hepatoma cells to sorafenib, thereby indicating the possibility of application of miRNA-loaded MSC-EV in liver cancer therapy [133].

Another type of MSC-EV engineered with miRNA targets PD-L1 and CTLA-4 to increase the anti-tumor immune response in immunotherapy [134]. Jiang et al. showed miR-9 and miR-181a bind to suppressor of cytokine signaling (SOCS3) and protein

inhibitors of activated STAT 3 (PIAS3), respectively. Otherwise, the more loosely structured SOCS and PIAS proteins will bind in place of SHP1/2 to inhibit activation of downstream JAK/STAT signaling that plays a role in MDSC development and prevents suppressor cell-induced T cell suppression [135]. In line with these results, other miRNA alterations were shown to confer anti-tumour effects on MSC-EVs in several cancer types. For instance, MSCs from Wharton's jelly were transfected with miR-124 to produce EV, increasing the temozolomide sensitivity in glioblastoma cells and reducing migration [136]. They similarly used EVs derived from rat brain MSC overexpressing miR-146b reduced glioma xenograft tumor burden. When cell-free EVs were applied in situ to the tumor cells, miR-146b delivery also reduced glioma growth at this location. Further, it confirmed the value of the MSC-EV-mediated miRNA transfer as a versatile tool for enhancing cancer therapy [99] (Table 1).

5. Mechanisms of action of MSC-EV-mediated Mirna delivery

5.1. miRNA-mediated gene regulation

MicroRNAs (miRNA) function in gene expression, particularly important for cancer development [145]. MiRNAs are thought to target complementary sequences in the 3′ untranslated regions (UTRs) of their mRNA targets, resulting in either mRNA degradation or translational repression [146]. In this case, miRNAs are delivered by MSC-EVs into the targeted cancer cell, allowing specific gene expression regulation, which is used to provide a regulated control via this regulatory mechanism in combination with their standard therapy for anticipating tumors [147].

EVs derived from MSCs are also enriched in miRNAs and can modulate many signaling pathways important for cancer development/progression. A typical example is the tumor suppressor miR-34a. One of the downstream targets of miR-34a is BCL and SIRT1 in cancer Stem cells, which are pro-survival proliferation genes. As a molecular switch for tumor development, miR-34a promotes apoptosis and suppresses cancer cell growth by downregulating these genes [148]. The other important molecular pathway modulated by the delivery of miRNA mimetics is the PI3K/AKT/mTOR pathway, which plays crucial roles in cell growth and proliferation and regulates metabolism. MSC-EVs deliver an engineered miR-122, which has been demonstrated to downregulate PI3K expression specifically. This downregulation inhibits the PI3K/AKT/mTOR pathway (which results in cancer cell proliferation) and, hence, a decrease in cancer malignancy [149].

Additionally, miR-200c is one example of an important miRNA for developing therapeutic strategies. This siRNA also specifically and efficiently downregulated the EMT-driving transcriptional repressors ZEB1 and sZEB2. By suppressing EMT, miR-200c transfer through MSC EVs can effectively decrease cancer cell metastatic potential and prevent aggressive behaviors in breast carcinoma [150]. These examples illustrate the diverse mechanisms through which miRNA-mediated gene regulation via MSC-EVs can be leveraged to target and disrupt key pathways in cancer, offering a targeted and efficient approach to cancer therapy [151].

5.2. Immune modulation

In addition to their existence in the tumor cells, miRNAs loaded on MSC-EVs seem capable of substantially influencing innate and

Table 1
The table summarizes MSC-derived exosomes delivering miRNAs in cancer therapy, highlighting key cargo, effects, and mechanisms.

EV Source	Cancer	Method	Key Cargo	Effect	Proposed Mechanism	Reference
hBMSC-derived exosomes	Breast cancer	In vitro and in vivo studies	miR-221-3p, miR-16	Suppression of angiogenesis and tumor growth	miR-16-mediated suppression of VEGF expression	[91]
hBMSC-derived exosomes	Breast cancer	In vitro studies	miR-100	Suppression of angiogenesis	Reduced VEGF levels, mTOR/HIF-1α signaling	[137]
hBMSC-derived exosomes	Breast cancer	In vitro studies	miR-23b	Induced dormancy in BM2 breast cancer cells	Targeting MARCKS, involved in cell cycling and motility	[138]
hBMSC-derived exosomes	Osteosarcoma	In vitro studies	miR-143	Inhibition of invasion and proliferation of osteosarcoma cells	Targeting invasion and proliferation pathways	[139]
hBMSC-derived exosomes	CRC	In vitro studies	miR-34a-5p	Suppression of cell growth and induction of apoptosis in CRC cells	Downregulation of c-MYC/DNMT3a/PTEN signalling pathway	[96]
hBMSC-derived exosomes	Brain tumors (glioma)	In vitro and in vivo studies	miR-146b	Decrease in glioma cell growth and xenograft tumor burden	miR-146b-mediated anti-tumor activity	[140]
hMSC-derived exosomes	Glioma	In vitro studies	miRNA-584-5p	Suppression of proliferation and migration, induction of apoptosis in glioma cells	Targeting Cytochrome P450 2J2 (CYP2J2) and inhibiting the Akt/MAPK pathway	[141]
hMSC-derived exosomes	Glioma	In vivo studies	miR-375	Reduction in glioma tumor growth	Inhibition of SLC31A1 expression	[142]
BMSC-derived exosomes	Glioblastoma	In vitro and in vivo studies	miR-512	Inhibition of glioblastoma cell proliferation, migration, and invasion	Downregulation of JAG1	[102]
hBMSC-derived exosomes	Multiple myeloma	In vitro and in vivo studies	miR-15a	Induction of tumor-related activities	Loss of tumor-suppressor activity due to decreased miR-15a levels	[105]
hBMSC-derived exosomes	Lung cancer	In vitro and in vivo studies	Let-7i	Suppression of lung cancer cell growth	Targeting the KDM3A/DCLK1/FXYD3 axis	[143]
hBMSC-derived exosomes	Prostate cancer	In vitro and in vivo studies	miRNA-145	Inhibition of prostate cancer development	Activation of caspase-3/7 pathway	[105]
hMSC-derived exosomes	Glioblastoma	In vitro and in vivo studies	miR-146b	Reduction of glioma growth in situ and tumor burden	miR-146b delivery and inhibition of tumor growth	[140]
hUCMSC-derived exosomes	Lung adenocarcinoma	In vitro studies	miRNA-410	Promotion of lung adenocarcinoma growth	Targeting PTEN, negatively regulating cell proliferation and apoptosis	[144]
hUCMSC-derived exosomes	Lung cancer	In vitro studies	miR-130b-3p	Promotion of lung cancer cell survival and proliferation	Modulating the FOXO3/NFE2L2/TXNRD1 axis	[113]

adaptive immune responses within TMEs (e.g., facilitating an anti-tumor immunity status), boosting therapeutic efficacy against cancer [152]. Tumor microenvironment or TME is the complex & dynamic interface of cancer cells with stromal/immune/ECM components. MSC-EVs can modulate the TME to be less conducive for tumor growth and adopt more supportive anti-tumor immune activity by reprogramming microenvironmental cells through delivering specific miRNAs [153]. For example, Chang et al. showed that miR-125b-enriched MSC-EVs could suppress angiogenesis in Triple-negative breast cancer (TNBC) by targeting endothelial VEGF and reducing its levels. The tumor's blood supply is reduced, and this leads to a decrease in angiogenesis, which limits the growth of the cancer as well as its ability to metastasize (spread around throughout) [154].

MSC-EVs with miRNAs can also contact other cells in their TME, such as DCs or macrophages and T-cells, to affect them towards anti-tumor immunity [155]. Pers et al. revealed that Dendritic cells loaded with miR-155−containing MSC-EVs enhanced dendritic cell activation and subsequently provided superior antigen presentation and greater cytotoxic T-cell activation. This enhanced immune response helps the immune system spot and destroy the cancer cells [156]. More research has shown transplantation of hPT-MSC-EVs can suppress IMQ-induced activation and reduce inflammatory cytokines expression in HMC-1 cells through transferring the miRNAs, especially has-miR-214−3p or hey-miR424−5p [157]. According to the Lin et al. associated with mast cell degranulation and releasing IL-1β, TNF-α, and IL-6 on KU812 cell lines activated by IgE were obstructed through NF-kB targeted-downregulated post-treatment using hUC-MSC-EVs according to the Lin et al. Moreover, hUC-MSC-EVs inhibited IgE-induced STAT5 phosphorylation in KU812 cells and showed dose-dependent inhibition of mast cell activation, leading to the reduction of allergic reactions through multifaceted mechanisms [158].

Macrophages, white blood cells adaptable to the immune system, recognize, engulf, and digest microbes and dead cells [159]. They also majorly affect inflammation, tissue repair, and immunity [160]. The functional roles of macrophages may affect their participation in several diseases, including cancer, as they can exist either in an anti-inflammatory M2 state or a pro-inflammatory M1 state [161]. In cancer, TAMs support tumor progression through inflammation activation, angiogenesis/extracellular matrix remodeling facilitation, and immunosuppression induction, which results in immune evasion [161]. These properties make TAMs attractive target components and critical determinants for cancer therapy [162]. Li et al. found that exosomes enriched with miR-181c effectively down-regulate burn-induced inflammation via the TLR4 signaling pathway. miR-181c or TLR4 knockdown reduced inflammation and inflammatory markers in burned rats [163]. Moreover, Li et al. discovered that EVs derived from hUCMSCs can effectively regulate inflammation and encourage macrophage polarization toward the M2 phenotype, further highlighting their role in modulating immune responses within the TME [164].

Because T cells participate in numerous immune-related activities, they are considered the hub of the immune response [165]. These cells can directly induce target cell death, regulate B cell antibodies, and produce lymphokines once adaptive immunity has been activated [166]. These interactions are critical to coordinating an immune response to pathogens and sickened cells [167]. According to Zhang et al. M yD88-dependent SEAP expression triggered showed that MSC-derived exosomes have immunological activity. These exosomes raised anti-inflammatory IL-10 and TGF-β1 while lowering pro-inflammatory IL-1β, IL-6, TNF-α, and IL-12p40 cytokines revealed to inactivate Myd88 molding exosome-treated THP-1 into CD4 + T cells. Regulatory T cells are critical in maintaining immunological tolerance and avoiding autoimmunity [168]. MSC-secreted EVs feature or affect many active proteins on their surface, including TSG-6, TGF-β, adenosine, CD73, PD-L1, GM-CSF, and β-catenin, all of which contribute to T cell upregulation [169]. For instance, TSG-6 in cAD-MSC-EVs is critical in increasing Tregs through upregulating FOXP3 [170]. TGF-β on BM-MSCs-EVs decreases the Th17 and enhances FoxP3+ Tregs in GAD65-treated PBMCs [171]. Further, TGF-β in hEND-MSCs-EVs substantially stifles the $CD4^+$ T cell activation [172]. Mokarizadeh et al. stated that the MSCs-MVs express TGF-β, galectin-1, and PD-L1, which suppress the proliferation of autoreactive lymphocytes and foster anti-inflammatory cytokine generation. The effect of MVs on immunoregulation is augmented under inflammation, which makes them relevant, for example, in cancer treatment [173]. Inhibitory effects of exosomes derived from bmMSCs were analyzed on the proliferation rate of activated B cells, T cells, and peripheral blood mononuclear cells (PBMC) as follows: 18 %, 23 %, and 37 %, respectively. Deep mRNA profiling was performed on B-lymphocytes treated with these exosomes, revealing 186 differentially expressed genes and highlighting their important role in immune functions [174]. Crain et al. identified that the EVs derived from canine Wharton's jelly MSC (WJ-MSC) suppressed $CD4^+$ T cell proliferation via transforming growth factor beta 1 and adenosine signaling pathways. These EVs from WJ-MSC were 125 nm in diameter, had a low buoyant density and expressed the extracellular vesicle protein markers Alix and TSG101. T cell proliferation was suppressed in a dose-dependent manner, and this effect was abrogated in samples depleted of EVs or those with non-MSC fibroblast-derived EVs. Suppression by IFN-γ was also blocked with the use of TGF-βRI antagonists, neutralizing antibodies to TGF-β or blocking A2A adenosine receptor (Fig. 3; Table 2) [175].

6. Contradictory studies on MSC-EV MiRNA delivery and cancer progression

Some studies observed contradictory opinions on the therapeutic effects of miRNAs in cancer treatment carried by exosomes released from MSCs [181]. As reports indicate that similar exosomes are capable of favoring tumor formation but also exhibit the ability to inhibit tumors in vitro and abrogate hematogenous local metastases under their miRNA cargo, miR-126 identified here may represent a dual cooperative/suppressive growth-promoting molecule [182] Qin et al. illustrated that miR-208a promoted cell proliferation, migration, and clonogenicity by targeting PDCD4 and activating the ERK1/2 pathway. The present study highlights the Role of BMSC-derived exosomal miR-208a in osteosarcoma progression [183].

Similarly, De Veirman et al. examined miRNA expression profiles in MSCs treated with multiple myeloma (MM) cell-conditioned medium and found that 19 of them were deregulated and upregulated miR-146a. They discovered that exosomal miR-146a from MM cells increased cytokine secretion in MSCs, and subsequently, activation of NFkB or IL6/STAT3 pathway was promoted, increasing MM cell viability and migration. This reciprocal stimulating loop, governed by the Notch pathway, powerfully reinforces MM development [184]. In addition, exosomes from BM-MSCs with miR-142-3p upregulation increased the fraction of CSCs in colon cancer, which Li and Li reported. Removing miR-142-3p from these exosomes decreased the CSC abundance, thus implicating that upon targeting Numb by this oncogenic miRNA, it enhances Notch signaling and contributes to cancer progression [185].

In contrast, in other studies, miRNA-containing exosomes derived from MSCs have been found to promote anti-tumor effects [186]. Roccaro et al. observed that exosomes derived from MM patient BM-MSCs enhanced the growth of their tumor by transferring oncogenic proteins, cytokines, and adhesive molecules to MM cells. In contrast, exosomes from normal BM-MSCs inhibited

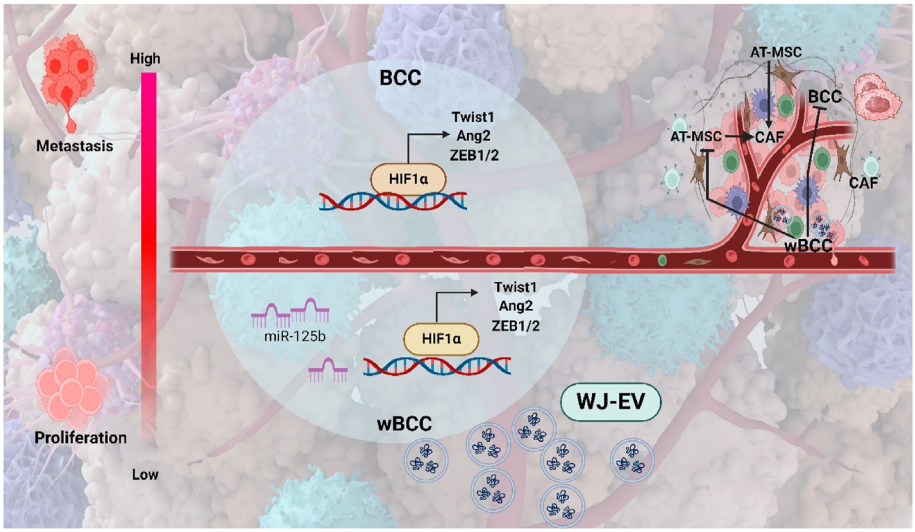

Fig. 3. The image illustrates interactions between breast cancer cells (BCC), white blood cancer cells (WBC), and their microenvironment, highlighting HIF1α's role in promoting metastasis via Twist1, Ang2, and ZEB1/2 pathways. WJ-EVs and miR-125b modulate these processes, affecting cancer progression.

MM cell growth. Of note, the exosomes derived from MM BM-MSCs showed a reduced expression of the downregulated factor miR-15a, thus an additional unique mechanism by which BMMSCs contribute to tumor progression [115,187]. Consistent with these observations, Wan et al. have also reported the anti-tumor effect of MSC-derived exosomes. Showed that miR-34c, a tumor-suppressive miRNA, could sensitize nasopharyngeal carcinomas (NPCs) to α-radiation by targeting β-Catenin. Mechanistically, exosomes derived from miR-34c-overexpression MSCs reduced NPC invasion and migration ability and suppressed cellular growth but increased the radiation-induced apoptosis of NPC cells [188,189].

Similarly, Lou et al. showed that miR-122-transfected adipose tissue-derived MSC exosomes (122-Exo) could efficiently deliver miRNA to HCC cells and sensitize them toward chemotherapeutic agents. MiR-122 also sensitized the targets in HCC cells to sorafenib and enhanced its anti-tumor activity on xenograft models [133,190]. These findings indicate that exosomes from MSC might be combined with more traditional cancer therapies, such as chemotherapy and radiotherapy. Or implemented to either promote tumorigenesis or inhibit tumor progression [191]. This duality highlights a dual sword miRNA-mediated regulation in cancer, prompting caution in therapeutic applications [192,193].

7. Challenges and considerations

One of the major obstacles in applying MSC-EVs as a therapeutic is their isolation and purification [194]. Even though approaches like differential centrifugation, density gradient separation, or size-exclusion chromatography are well established (although not

Table 2
The table categorizes MSC-derived exosomes by their functional roles in cancer therapy, highlighting miRNA targets, pathways, and effects.

EV Source/Condition	miRNA	Expression	Target	Pathway	Effect	Reference
MSC-EVs in apoptosis regulation	miR-34a	Downregulated	BCL, SIRT1	Apoptosis	Promotes apoptosis, suppresses cancer cell growth	[148]
MSC-EVs in cancer proliferation	miR-122	Downregulated	PI3K	PI3K/AKT/mTOR	Decreases cancer malignancy	[176]
MSC-EVs in metastasis inhibition	miR-200c	Downregulated	ZEB1, ZEB2	EMT suppression	Decreases metastatic potential	[177]
MSC-EVs in angiogenesis suppression	miR-125b	Enriched	VEGF	Angiogenesis	Suppresses angiogenesis	[154]
MSC-EVs in immune modulation	miR-146a-5p	Engineered	IL6, TNFα	Immune modulation	Reduces inflammatory cytokines	[178]
MSC-EVs in immune activation	miR-155	Loaded	Dendritic cells	Antigen presentation, cytotoxic T-cell activation	Enhances immune response	[156]
MSC-EVs in inflammation reduction	miR-181c	Enriched	TLR4	TLR4 signaling	Reduces inflammation	[163]
MSC-EVs in cytokine suppression	miR-214-3p	Transferred	Inflammatory cytokines	NF-kB targeted-downregulation	Suppresses IL-1β, TNF-α, IL-6	[158]
MSC-EVs in mast cell regulation	miR-424-5p	Transferred	Inflammatory cytokines	STAT5 phosphorylation	Inhibits mast cell activation	[158]
MSC-EVs in immune response modulation	miR-181c	Knockdown	TLR4	TLR4 signalling	Reduces inflammation and inflammatory markers	[163]
MSC-EVs in MyD88 signaling modulation	miR-10	Raised	IL-1β, IL-6, TNF-α, IL-12p40	MyD88-dependent SEAP expression	Inactivates Myd88, molding exosome-treated THP-1	[179]
MSC-EVs in T-cell proliferation inhibition	TGF-β	Expressed	$CD4^+$ T cells	T Cell activation	Suppresses $CD4^+$ T cell proliferation	[180]
MSC-EVs in Treg upregulation	TSG-6	Present	FOXP3	Tregs upregulation	Increases Tregs	[174]
MSC-EVs in T cell activation suppression	TGF-β	Stifled	$CD4^+$ T cells	Th17 downregulation, Tregs upregulation	Suppresses $CD4^+$ T cell activation	[175]

without limitation), each has some deficits. Although differential centrifugation is a routine exclusionary step, MSC-EV isolates can include cellular debris and protein aggregates that could contaminate the purity of EVs, affecting functionality [195,196]. Density gradient centrifugation improves purity but is more labor-intensive and equipment-demanding [197]. Though size exclusion chromatography is exceptionally mild for the vesicles themselves, it will also holistically separate all and any contaminants in the solution [198,199]. Until cell therapy products become standardized, the isolation protocols must be normalized to ensure consistent quality and reproducibility of MSC-EVs [200]. In addition, scalable isolation methods are required to produce enough MSC-EVs to be suitable for clinical use. However, developing automated and high-throughput isolation systems could alleviate these problems by increasing productivity and feasibility for expansion in the production of MSC-EVs [201,202].

The stability and bioavailability of miRNAs in MSC-EVs are necessary for the therapeutic function as a delivery route [203]. Encapsulated miRNAs must be stable during storage, transportation, and administration [204]. The inherent stability of miRNAs is also protected from enzymatic degradation by the protective lipid bilayer that encapsulates MSC-EVs [205]. However, temperature, PH, or storage should be considered to preserve miRNA intact [206]. Researchers are also studying stabilizing agents and better storage conditions to improve miRNA stability within MSC-EVs [207,208]. Lyophilization (freeze-drying), another option, may enhance the long-term stability of MSC-EVs by removing water content and slowing down their degradation. In addition, altering the lipidome of MSC-EVs to be more saturated with stable lipids would likely improve this hitherto less sustainable miRNA-such approach [41,209]. Moreover, it isn't easy to ensure that miRNAs are available at the target site (bioavailability) once administered, which means the delivery system should release them properly there [210]. The release kinetics of miRNAs from MSC-EVs may be dictated by the microenvironment within the target tissue [211,212].

The safe use of MSC-EVs for miRNA delivery in the clinical setting raises multiple safety concerns that must be considered [212,213]. Another concern is the immunogenicity of MSC-EVs [214]. As much as MSC-EVs are supposed to be non- or low-immunogenic, remnants of proteins/contaminants from the isolation procedure might spur immune responses [215]. Therefore, obtaining high-purity MSC-EVs is crucial to mitigate the risk of complications. One has to do with off-target effects. However, because miRNAs can regulate many genes and pathways simultaneously, they also pose a danger of deregulating other non-cancerous cells in the body, leading to unwanted side effects like impairing normal cellular functions [145,216]. Alternatively, to reduce variable MSC-EV targeting and lower miRNA off-target risk/profile, we could have MCS-EV engineered with some affinity ligands (e.g., proteins) that bind cancer cells explicitly, ensuring higher local concentration at targeted local that subsequently leads to less toxicity than systemically delivered EVs securing increase the precision in miRNA delivery as well [217,218]. Moreover, one consideration with using MSC-EVs is long-term safety; if these vesicles and their miRNA cargo linger in the body, there might be some unforeseen consequences [219].

8. Future directions and clinical implications

EV engineering has emerged as a novel field in EV-based miRNA therapy. However, continuous research is required to improve the delivery efficiency and therapeutic efficacy of MSC-EVs for this purpose [220,221]. These modifications include genetic and chemical alterations to improve miRNAs' targeting specificity, stability, and bioavailability [222]. One way to improve the function of their derived EVs is by applying genetic engineering in MSCs [223]. MSC-EV surface can be modified by targeting ligands specific for cancer cell receptors by transfecting MSCs with plasmids carrying protein or peptide genes [224,225]. For instance, engineered MSC-EVs expressing EGFR ligands can target tumors that over-express the EGFR, including some breast and lung cancers [226]. These miRNAs can be delivered to the tumor site precisely and specifically by being loaded into potentially off-target-free MSC-EVs, thus achieving maximal therapeutic effect [227,228]. Research investigating the use of chemical modifications to increase stability and delivery efficiency is also ongoing in MSC-EVs. Surface modification with polyethylene glycol can extend the circulation time of MSC-EVs in blood by avoiding opsonization and immune system-mediated clearance [68,229]. Moreover, introducing pH-sensitive or enzyme-cleavable linkers in this MSC-EV structure could also improve the on-demand release capacity of miRNAs within the TME to increase therapeutic efficacy and specificity.

MSC-EV-mediated miRNA therapy is only beginning to be translated clinically; however, several encouraging studies have been conducted [230]. In the context of cancer disease progressions, clinical trials are ongoing to assess spectra safety and preliminary efficacy of MSC-EVs for the delivery of therapeutic miRNAs [231,232]. These trials are intended to collect crucial data on MSC-EV based-therapeutic products' pharmacokinetic, biodistribution, and safety profiles [233,234]. A phase I clinical trial for glioblastoma patients with miR-124-loaded MSC-EVs. This study examines the safety and feasibility of targeting miR-124, a tumor-suppressor miRNA, directly in brain tumors using MSC-EVs [235,236]. Developed Further There is also an ongoing clinical trial in liver cancer patients to assess the efficacy of MSC-EVs loaded with miR-122. This study aims to determine the potential of MSC EVs carrying miR-122 to improve liver cancer cells' sensitivity to Sorafenib. These preliminary data indicate that delivering tumor-associated miRNAs via MSC-EVs may enhance treatment responses and limit growth in this model [237,238].

9. Conclusion

In the context of the presently underdeveloped field of using mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) as nanocarriers for miRNA delivery in cancer therapy, the review manuscript contributes a major leap forward to this area. Though prior studies have discussed the delivery systems of miRNA, this manuscript is novel, encompassing recent expansion and improvement of MSC-EV in terms of therapeutic targeting, stability, and efficiency. Compared with synthetic NP and virus, MSC-EVs themselves own low immunogenicity and inherent biocompatibility, and thus have the ability of accurate tumor homing with minimal side effects. Compared to previous studies, this one focuses on innovative approaches, including electroporation and ligand-based surface change for enhanced miRNA loading and delivery. Together the manuscript offers the latest perspective on challenges like miRNA stability throughout storage and its availability to the target tumor cells. Besides, the review provides a critical evaluation of preclinical evidence showing that MSC-EVs may prevent tumor development, and metastatic progression and improve other therapies including chemotherapy and radiotherapy. With these achievements, and the challenges of isolation, scalability, and safety, the manuscript outlines further development for clinical application and confirms MSC-EVs as a novel next-generation therapeutic platform for targeted oncology. This review offers an essential milestone for the future of MSC-EV-based cancer treatment.

Author contributions

AKB, MAB, MA, and GS: Conceptualization, Methodology, Software. RMM, SG, and MR: Writing – Original Draft Preparation. HA

and KG: Data curation, Writing – Review & Editing. VS: Data Curation and Methodology. LSW: Methodology, Software. VK: Conceptualization, Methodology, Software.

Data availability

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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