

## REVIEW

# Research progress on exosomes derived from mesenchymal stem cells in hematological malignancies

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## Abstract

Mesenchymal stem cells (MSCs) are a subset of multifunctional stem cells with self-renewal and multidirectional differentiation properties that play a pivotal role in tumor progression. MSCs are reported to exert biological functions by secreting specialized vesicles, known as exosomes, with tumor cells. Exosomes participate in material and information exchange between cells and are crucial in multiple physiological and pathological processes. This study provides a comprehensive overview of the roles, mechanisms of action and sources of MSC exosomes in hematological malignancies, and different tumor types.

## KEYWORDS

exosome, hematological malignancy, mesenchymal stem cell

## 1 | INTRODUCTION

Mesenchymal stem cells (MSCs), an important component of the bone marrow (BM) microenvironment, display a high degree of heterogeneity along with the potential of self-renewal and multidirectional differentiation into several cell types, such as osteoblasts, chondrocytes, adipocytes, and tissue macrophage-like cells.<sup>1-3</sup> These specialized cells have several functions, including production of multiple growth factors and chemokines, participation in signaling pathways mediated by cell-cell contact, regulation of the BM microenvironment, and promotion of self-renewal, homing, proliferation, and differentiation of hematopoietic stem/progenitor cells.<sup>4</sup> MSCs are additionally reported to migrate to primary and metastatic tumors and exert inhibitory effects on tumor cell proliferation and cancer progression.<sup>5</sup> Evidence that BM MSCs promote growth of multiple myeloma (MM) cells through stimulating production of their major growth factor, interleukin-6 (IL-6), has been documented.<sup>6</sup> Consistently, growth and accumulation of leukemic cells are closely related to MSCs in the BM microenvironment. MSCs have been shown to enhance leukemic cell survival by increasing

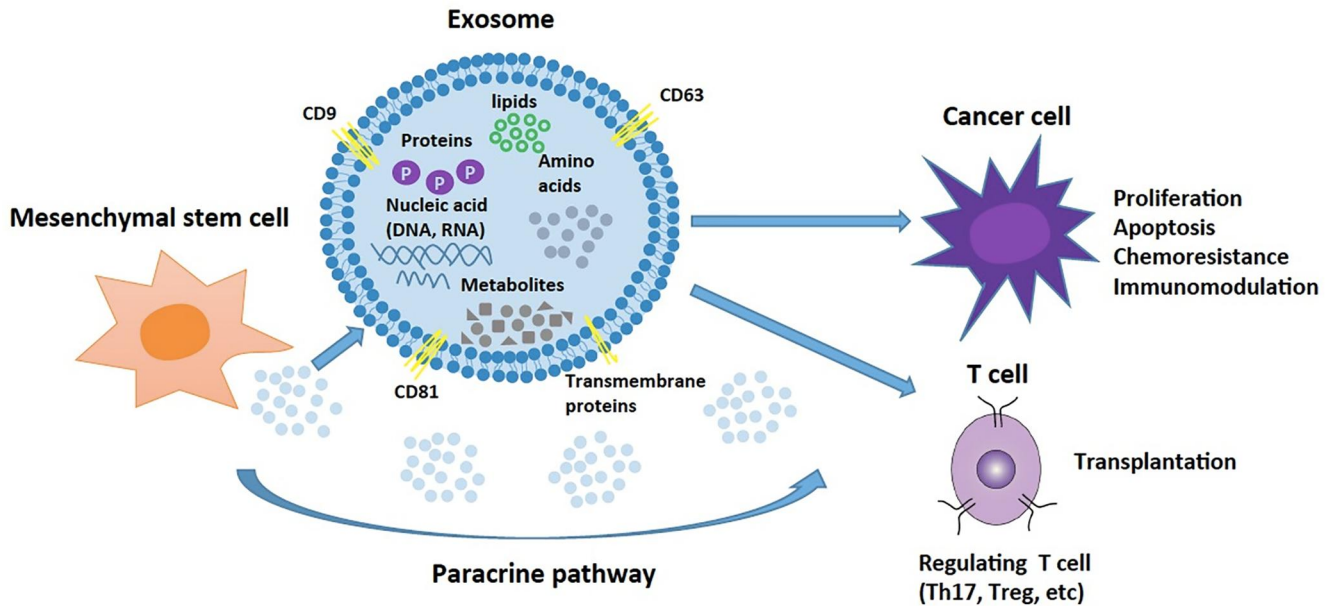
the expression of hepatocyte growth factor and CXC chemokine ligand 12 and inhibit leukemic cell apoptosis through Notch-3 and other signaling pathways.<sup>7</sup> In contrast, other *in vitro* studies suggest that MSCs can suppress progression of leukemia and lymphoma cell growth and reduce IL-10 secretion through cell cycle arrest.<sup>8</sup> The collective results indicate that MSCs act as a double-edged sword to exert either pro- or anti-tumor effects. Moreover, in co-cultures of MSCs and hematological malignant cells, the cell types interact directly through secretion of both soluble factors and exosomes.<sup>9-12</sup>

## 2 | EXOSOME BIOGENESIS

Exosomes are specific microvesicles released into the extracellular environment after fusion of intracellular polyvesicles and membranes of living cells. These vesicles have a double-layered membrane structure with diameters ranging from of ~40 to 160 nm.<sup>13</sup> Following invagination of the cell membrane, intracellular vesicles are formed, which receive part of the cytoplasm and generate early

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**FIGURE 1** Function of exosomes derived from mesenchymal stem cells on hematological malignant cells. Exosomes could be derived from mesenchymal stem cells, affecting the proliferation, apoptosis, chemoresistance and immunomodulation of cancer cells as well as transplantation of T cells

nuclear endosomes. Next, endosomal sorting complexes required for transport (ESCRT)-0 recruit ubiquitin proteins and ESCRT-I and ESCRT-II induce the inner membrane to sprout inwards to form various intraluminal vesicles (ILVs). Late endonucleosomes containing ILVs are generated, known as multivesicular bodies (MVBs). Mature MVBs are degraded after binding to lysosomes or fused with cell membranes to release ILVs to the extracellular environment via exocytosis. These ILVs are exosomes that, upon contact with receptor cells, immediately activate signaling pathways related to their cell surface proteins or activating cascade reactions within cells that affect cellular function or behavior through fusion transfer of exosomal proteins, miRNAs, mRNAs, and other active substances.<sup>14,15</sup>

Secreted exosomes participate in cell-cell material and information exchange and play key roles in several physiological and pathological processes.<sup>16</sup> In recent years, the interactions between MSC-derived exosomes and hematological malignancies have attracted increasing research attention. The latest developments are reviewed in this study (Figure 1).

### 3 | EFFECTS OF MSC-EXO ON PROLIFERATION AND APOPTOSIS OF HEMATOLOGICAL MALIGNANCIES

The BM microenvironment promotes the survival and proliferation of tumor cells mainly through interactions with MSCs. An ex vivo study by Wang et al.<sup>17</sup> showed that MM BM-MSC-exos and normal donor (ND) BM-MSC-exos promote MM cell proliferation and affect several

survival-related signaling pathways, such as c-Jun N-terminal kinase, p38, p53, and Akt, which was further verified in a murine 5T33MM model. In a study by Deng et al.,<sup>18</sup> LINC00461 secreted by MM-MSC-exos targeted miR-15a/16 and regulated the B-cell lymphoma-2 oncogene to enhance MM cell proliferation. MM BM-MSC-exos was further shown to promote MM cell growth and spread in vivo by Roccaro et al.<sup>19</sup> The group of Chemel showed that MSC-exos can stimulate receptor cells without targeting but contains interleukin-34 (IL-34) that induces strong,<sup>20</sup> transient tyrosine phosphorylation and activation of specific colony-stimulating factor 1 receptor (CSF1R) in chronic lymphocytic leukemia cells.<sup>21,22</sup> Increase in CSF1R activity leads to activation of the c-ruf-1 proto-oncogene, in turn, promoting serine/threonine kinase activity, signaling pathways of intracellular growth stimulation, and continuous cell growth and proliferation.<sup>23</sup> Evidence showed that IL-34 enhances infiltration of tumor-associated macrophages, which release nutritional factors to tumor cells that promote angiogenesis and metastasis and are significantly associated with poor prognosis.<sup>24,25</sup> In addition, BM-MSC-exo directly targeted the IRF2 gene by secreting miR-222-3p, thus negatively regulated the IRF2/INPP4B pathway in THP-1 cells, leading to suppression of leukemia cell proliferation, promotion of apoptosis and prevention of leukemia progression.<sup>26</sup> Interestingly, human umbilical cord (UC) MSC-exos are reported to exert no effects on proliferation and apoptosis of K562 cells but boost apoptosis induced by imatinib for increasing the Bax and decreased Bcl-2 expression.<sup>27</sup> In other words, exosomes enhance the sensitivity of K562 cells to imatinib by activating a caspase signaling pathway. The collective findings indicate that MSC-exos contribute significantly to either promotion or inhibition of hematological malignancies (Table 1).

TABLE 1 Studies on the double-edged sword effects of MSC-exo in hematological malignancies

Source of exosome	Recipient cell	Model	Conclusion	References
Murine BM-MSC MM BM-MSC ND BM-MSC	MM (5733MMvt and RPMI8226)	C57BL/KaLwRij	Activation of c-Jun N-terminal kinase, p38, p53, and Akt, increased MM cell growth, and induction of drug resistance to bortezomib	Wang et al. <sup>17</sup>
MM BM-MSC ND BM-MSC	MM (U266 and OPM-2)	-	MM cell proliferation is promoted through LINC00461 while LINC00461 relieves the inhibitory effect of miR-15a/miR-16 on BCL-2	Deng et al. <sup>18</sup>
Murine BM-MSC MM BM-MSC ND BM-MSC	MM (MM1S and RPMI8226)	SCID-beige and C57BL/6	MM BM-MSC-exo promotes MM tumor growth and ND BM-MSC-exo inhibits MM cell growth	Roccaro et al. <sup>19</sup>
ND BM-MSC	AML (THP-1)	-	ND BM-MSC-exo-miR-222-3p inhibit cell proliferation and promote apoptosis through targeting IRF2 and negatively regulating IRF2/INPP4B signaling in THP-1 cells	Zhang et al. <sup>26</sup>
ND UC-MSC	CML (K562)	-	Sensitivity of K562 cells to IM is enhanced via activation of caspase signaling	Liu et al. <sup>55</sup>
MM BM-MSC	MM (MM1S and U266)	NSG	Exo-PSMA3/LncPSMA3-AS1 play a role in transmitting PIs (bortezomib) resistance from MM BM-MSCs to MM cells	Xu et al. <sup>28</sup>
AML BM-MSC ND BM-MSC	AML (MOLM-14)	-	Differential protection against kinase pathway inhibition observed only with AML BM-MSC-exo	Viola et al. <sup>29</sup>
AML BM-MSC HS5	AML (KG1a, NB4, and MV411)	-	Exosome repression in a BMSC and AML co-cultivating system restores sensitivity of KG1a cells to apoptosis triggered via etoposide	Chen et al. <sup>30</sup>
OP9 ND BM-MSC	ALL pre-B	C57Bl/6J	Activation of the NF- $\kappa$ B pathway and auto-induction of Galectin-3 mRNA and MSC-exo-Galectin-3 protect ALL cells from the effects of nilotinib and vincristine	Fei et al. <sup>31</sup>

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid Leukemia; BM, bone marrow; BMSC, bone marrow mesenchymal stem cell; CML, chronic myeloid leukemia; exo, exosome; IM, imatinib mesilate; MM, multiple myeloma; MSC, mesenchymal stem cell; ND, normal donor; NSG, nod/scid/il2ry-/-; SCID, severe combined immunodeficiency disease; UC, umbilical cord.

#### 4 | EFFECTS OF MSC-EXO ON CHEMOTHERAPEUTIC RESISTANCE OF HEMATOLOGICAL MALIGNANCIES

Resistance of tumor cells to chemotherapeutic drugs (including primary and secondary drug resistance) is the major cause of treatment failure of hematological malignancies. Secondary drug resistance induced by MSC-exos is a potential mechanism underlying tumor heterogeneity. For instance, exosome-mediated transfer of encoding proteasome subunit  $\alpha 3$  (PSMA3) and LncPSMA3-AS1 from BM-MSCs to MM cells is implicated in the mechanism of drug resistance of MM cells to bortezomib.<sup>28</sup> In xenograft models, knockout of the LncPSMA3-AS1 gene effectively increased sensitivity of cells to carfilzomib. The BM-MSC-exos-mediated PSMA3-AS1/PSMA3 pathway plays a unique role in drug resistance of MM cells to proteasome inhibitors. In keeping with these findings, Wang et al.<sup>17</sup> showed that BM-MSC-exos enhances the resistance of MM cells to bortezomib in a murine 5T33MM model. Moreover, Viola et al.<sup>29</sup> showed that MSC-exos trigger secondary drug resistance in the BM microenvironment of patients with acute myeloid leukemia (AML). The MOLM-14 FLT3 internal tandem duplicate (FLT3-ITD+) AML cell line was treated with the nucleoside analog,

cytarabine, used as the standard therapy for AML, and exposed to either AML-BM-MSC-exos or ND-BM-MSC-exosomes. Exosomes from both AML and ND patients (6 AML-BM-MSC and 4 ND-BM-MSC) induced resistance to cytarabine.

In view of the differential inhibitory effects on the kinase pathway, AML cells were further treated with the FLT3 inhibitor, AC220. In this case, AML-BM-MSC-exosomes retained the ability to protect AML cells against the effects of AC220, but not ND-BM-MSC-exos.<sup>29</sup> Similarly, in coculture systems of BM-MSCs and AML cells, derived exosomes rebuild the sensitivity of KG1 $\alpha$  cells to apoptosis induced by etoposide, providing further evidence that exosomes regulate AML sensitivity to chemotherapeutic drugs.<sup>30</sup> Fei et al.<sup>31</sup> reported the low expression of lectin galactose binding protein-3 (Gal-3) in B acute lymphoblastic leukemia (B-ALL) was significantly increased upon coculture of B-ALL and mouse BM stromal cells, suggesting the function of mouse BM stromal cells in synthesizing Gal-3 and encapsulating it in exosomes for transmission to B-ALL cells as well. Upon treatment of the MSC and ALL coculture systems with trametinib (an inhibitor of the extracellular regulated protein kinases [ERK] pathway) and BMS34541 (an inhibitor of the nuclear factor- $\kappa$ B [NF- $\kappa$ B] pathway), drug resistance mediated by Gal-3 was weakened to some extent,

leading to the speculation that Gal-3 causes drug resistance of ALL cells through Erk and NF- $\kappa$ B signal pathways. Viola et al. reported that relative to exosomes secreted by ND-MSC, those secreted by AML-MSC contained higher levels of miR155 and transforming growth factor beta 1 (TGF- $\beta$ 1), leading to elevated cell survival, proliferation and leukemia progression.<sup>29</sup> Buettner et al. identified increased miR155 levels as an independent prognostic factor affecting the recurrence of AML.<sup>32</sup> Inactivation of SHIP1, one of the targets of miR155, leads to continuous activation of the PI3K/AKT pathway,<sup>33</sup> which affects a variety of downstream effector molecules, inducing uncontrolled cell proliferation, inhibition of apoptosis, and promotion of malignant diseases.<sup>34</sup> In addition, exosomes released by AML stromal cells contain multiple known clinical risk factors, which downregulate promoters of apoptosis or differentiation through exosomal miRNA and release more leukemic cells in a kinase-dependent manner, ultimately leading to resistance to chemotherapy.

Therefore, exosome-mediated signal transduction systems inhibiting the kinase pathway present a key mechanism underlying exogenous chemotherapy resistance in the AML niche.<sup>35</sup> The collective reports suggest that MSC-exos not only regulate the tumor microenvironment to promote cell-cell interactions but also play a crucial role in tumor heterogeneity (Table 1).<sup>16</sup>

## 5 | EFFECTS OF MSC-EXO ON CELLULAR IMMUNITY OF HEMATOLOGICAL MALIGNANCIES

A number of studies have highlighted the clinical significance of the immunomodulatory function of BM-MSCs. Although the main regulatory pathways remain unclear, MSCs have immunosuppressive properties, which may be one of the main contributory factors to tumor cell growth in hematological malignancies.<sup>5</sup> MSCs affect the immune system by interacting with innate cellular components, such as natural killer (NK) cells, and adaptive cellular components, such as dendritic cells (DC), B lymphocytes and T lymphocytes.<sup>36</sup> Among these, a number of known immunomodulatory factors regulate the effects of BM-MSCs on tumor cells, including TGF- $\beta$ ,<sup>37,38</sup> interleukin-1 $\beta$  (IL-1 $\beta$ ),<sup>39</sup> and indoleamine 2,3-dioxygenase (IDO).<sup>40</sup> IL-1 $\beta$  is a major cytokine responsible for the innate and adaptive immune response. Elevation of IL-1 $\beta$  levels is a common event in hematological malignancy and reported as a biomarker of poor prognosis in AML. Blockage of IL-1 $\beta$  is therefore proposed as an effective strategy for AML therapy.<sup>41,42</sup> Similarly, a significant decrease in TGF- $\beta$  in AML has been reported, indicating an inhibitory effect of this cytokine on growth of leukemic cells. Decrease in the TGF- $\beta$  signal may contribute to AML cell survival, a common feature of many hematological malignancies.<sup>43</sup> Additionally, tumor necrosis factor (TNF)- $\alpha$  plays a critical positive role in chemotherapeutic resistance of leukemia cells and survival of leukemic clones. In contrast, exposure of normal hematopoietic stem cells (HSCs) to TNF- $\alpha$  has been shown to induce cell growth inhibition.<sup>44</sup> The collective findings suggest that cytokines exert opposite effects depending on the cellular

environment. Interestingly, upon coculture of MSC-exos with peripheral blood mononuclear cells (PBMCs), the concentrations of immunomodulatory factors IL-1 $\beta$  and TNF- $\alpha$  were decreased significantly while TGF- $\beta$  secretion was increased and no changes in IDO were evident.<sup>45</sup> Similarly, coculture of BM-MSC-exos with DC cells resulted in reduced release of cytokine IL-6, enhanced release of IL-10 and TGF- $\beta$ , and subsequently, reduced lymphocyte proliferation.<sup>46</sup> Several studies have shown that BM-MSC-exos not only inhibit activation of T cells and production of IFN- $\gamma$  but also proliferation of T, B and NK cells.<sup>47-51</sup> The results suggest that similar to MSCs, MSC-exos mediate progression of leukemia by regulating changes in immunomodulatory factors in cells. Another *in vitro* study showed that myeloid-derived suppressor cells (MDSCs) of MM could absorb BM-MSC-exos. Survival of MDSCs was directly promoted via activation of signal transducer and activator of transcription (STAT)-3 and STAT-1 signal pathways, leading to an increase in anti-apoptotic Bcl-xl and myeloid cell leukemia-1 (Mcl-1) levels and improved release of nitric oxide by suppressor cells, and consequently, enhancement of the inhibitory activity of T cells and MM progression.<sup>52</sup> Limited studies to date have investigated the immune regulatory effects of MSC exosomes in hematological malignancies and further research is warranted to clarify their roles in tumor growth.

## 6 | EFFECTS OF MSC-EXO ON STEM CELL TRANSPLANTATION FOR HEMATOLOGICAL MALIGNANCIES

For pretransplantation preconditioning, transplantation based on MSCs alone or in combination with HSCs can enhance survival rates and improve BM hematopoietic reconstitution after radiation injury.<sup>53-58</sup> The mechanisms of MSC tissue repair and remodeling are proposed to be related to their differentiation ability or paracrine effect.<sup>59,60</sup> Wen et al.<sup>61</sup> demonstrated the effects of extracellular vesicles (EV) derived from BM-MSCs on radiation-induced damage to BM stem cells at 4 h-7 days after radiotherapy. Moreover, administration of 500cGy radiation to the mouse HPC line, FDC-P1, effectively reversed growth inhibition, DNA damage and apoptosis induced by MSC-EV treatment in mice and humans, indicating that BM-MSC-EVs could reverse radiotherapy-induced damage to BM stem/progenitor cells. Similarly, BM-MSC-exos reduced radiation-induced bone loss *in vivo*. While the effects of BM-MSC-exos and BM-MSCs on transplantation are similar, BM-MSC-exos confer greater advantages, such as reduced oxidative stress, accelerated DNA damage repair, reduced inhibition of proliferation and cell senescence-related protein expression, leading to improved migration ability of recipient MSCs to damaged tissue and restoration of the balance between adipogenic and osteogenic differentiation. The data clearly indicate that BM-MSC-exos exert their effects by restoring the functions of recipient BM-MSCs.<sup>62</sup>

Graft versus host disease (GvHD) after transplantation can lead to serious complications that reduce quality of life of patients or

even result in death, limiting widespread use of this technique for hematological malignancies.<sup>63</sup> In 2004, Le Blanc et al.<sup>64</sup> introduced MSCs as a potential strategy to treat severe refractory acute GvHD (aGvHD). Since then, several investigations have focused on the utility of MSCs for GvHD, with variable results. The latest research indicates that MSCs mainly exert immunosuppressive effects by secreting immunomodulatory factors, such as IL-10, TGF- $\beta$ , and IDO, that partly exert their effects through cell-cell interactions.<sup>65</sup> Owing to the importance of paracrine mechanisms in the MSC effect, cell therapy can be replaced with cell-free therapy with low immunogenicity and high safety. As a novel type of cell-free therapy, exosomes significantly avoid polarization of MSCs under various disease conditions.<sup>66</sup> MSC-exos mediate the paracrine effect of MSCs, play an immunomodulatory role, promote tissue repair and restore dynamic balance, highlighting their potential benefits as cell-free therapy.<sup>67-71</sup> A study by Kordelas et al.<sup>72</sup> demonstrated significant improvement in clinical symptoms of GvHD patients shortly after initiation of MSC-exos treatment. Dal Collo et al. showed that use of BM-MSCEVs as an alternative to MSCs led to significant improvement in the incidence and progression of aGvHD in a mouse model and enhanced survival rates in mice.<sup>73</sup> In experiments by Fujii et al.<sup>74</sup> infusion of BM-MSCEVs prolonged survival times of aGvHD mice and reduced pathological damage to target organs, suggesting a unique immunomodulatory function of BM-MSCEVs. Zhang and coworkers additionally confirmed that MSC-exos effectively alleviate the symptoms of GvHD and improve survival of mice.<sup>75</sup> In view of these encouraging results, Wang et al.<sup>76</sup> examined the utility of MSC-EVs from different tissue sources in preventing aGvHD after allogeneic hematopoietic stem cell transplantation (allo-HSCT) in the murine model. Their experiments showed that UC-MSCEVs promoted the levels of anti-inflammatory cytokines while suppressing proinflammatory cytokines. They also illustrated expression of aGvHD and related histological changes, leading to significant reduction in the mortality of recipient mice. MSC-exos have additionally been applied to prevent and treat chronic GvHD (cGvHD). While not as harmful as aGvHD, this condition remains the main cause of long-term morbidity and mortality after allo-HSCT.<sup>77</sup>

Alloreactive T helper (Th) cells are abnormally activated, infiltrate and attack target organs, and induce formation of cGvHD via mechanisms in which Th1 and Th2 play key roles.<sup>78</sup> Accumulating studies have further focused on Th17 and regulatory T (Treg) cells involved in coordinating the immunopathological environment of cGvHD.<sup>79</sup> Regulation of abnormal T cell response may present an effective strategy to alleviate the pathological changes of cGvHD. Lai et al.<sup>80</sup> showed that MSC-exos block Th17 differentiation of PBMCs and improve their Treg phenotype in normal subjects and active cGvHD patients, further supporting a regulatory effect on GvHD effector T cells.

In addition, MSC-exos effectively prolonged survival times and reduced clinical and pathological scores of cGvHD mice.<sup>81</sup> Following MSC-exos treatment, expression of Th17 cell-related transcription factors and proinflammatory cytokines was significantly decreased,

along with marked improvement in fibrosis of skin, lung and liver in mice. Thus, MSC-exos exert a strong immunomodulatory effect during cGvHD through inhibiting pathogenic T cells expressing IL-17 and stimulating regulatory cells expressing IL-10. The collective findings in the literature support the utility of MSC-exos as a novel and safe therapeutic tool for the prevention and treatment of GvHD.

## 7 | CONCLUSIONS AND PERSPECTIVES

Exosomes are natural nanostructures that can effectively reach most tumor regions, including hypoxic areas. The ability of these vesicles to break through the complete vascular barrier and enter the systemic circulation reinforces their significance in tumor biology. Complex interactions between exosomes secreted by MSCs and tumors pose a considerable challenge in clarifying the mechanisms underlying tumor growth. MSC-exos play similar roles to MSCs in tumor progression. MSC-exos are assumed to have tumor-dependent functions and thus exert significantly contrasting effects. However, existing problems with quality control of the exosomes obtained or sample preparation may also lead to conflicting results. Therefore, development of effective quality control or standard operating procedures for exosome separation technologies is necessary to achieve experimental stability and uniformity. In addition, the differences in data may be attributed to variable times of MSC growth, compositions of culture medium, number of passages of MSC used, donor ages and MSC sources.<sup>82,83</sup> Experimental use of MSCs at low passage numbers and regulation of growth conditions is therefore essential to obtain consistent results with exosomes. Similarly, determination of the growth times of MSC-exos separation and quality of serum depleted of exosomes during MSC growth should be useful to obtain variable data. The sources of MSCs (UC and BM) may also alter the composition of exosome cargo, thus, influencing their effects on tumor cells. For example, human UC-MSCEVs enhance the sensitivity of K562 cells to imatinib by activating the caspase signaling pathway to achieve anti-tumor activity.<sup>27</sup> BM-MSCEVs repress apoptotic sensitivity of KG1a leukemic cells induced by etoposide in cocultures, indicating that exosomes regulate leukemic cell resistance to chemotherapeutic drugs to promote tumor growth.<sup>30</sup> Accordingly, the effects of MSC-exos systems from different sources on tumor cells cannot be equally compared. Effects on tumor cells of MSCs from different individuals must also be considered. For example, MM-MSCEVs facilitate MM cell proliferation while ND-MSCEVs suppress MM cell growth,<sup>19</sup> indicating that exosomes from different tissue sources and individuals have opposite effects on tumor cells. As secretion of exosomes is affected by multiple factors, changes in the external environment can also influence the number and function of MSC-exos. Hypoxia or stimulation with specific cytokines (such as TGF- $\beta$  or IFN- $\gamma$ ) may not significantly affect MSCs themselves. However, differences in exosome secretion exist and the number of exosomes secreted by cells may also increase, suggesting that

specific cytokines can be used to stimulate MSCs in vitro to obtain more effective immunomodulatory exosomes in the future.<sup>84-86</sup> Based on the collective findings, we reasonably conclude that MSC-exos are multifaceted tumor regulatory factors that may be effectively applied in the clinical treatment of cancer.

## CONFLICTS OF INTEREST

All authors declare no conflict of interest.

## ETHICAL APPROVAL

Being a review article, ethical committee approval was not required.

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## PEER REVIEW

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