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Authors: Carl Randall Harrell, Valentin Djonov and Vladislav Volarevic

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Mesenchymal stem cell-derived microRNAs: friends or foes of tumor cells?

Carl Randall Harrell[1], Valentin Djonov[2], and Vladislav Volarevic[3, 4*]

[1]Regenerative Processing Plant, LLC, 34176 US Highway 19 N, Palm Harbor, Florida, United States of America

[2]Institute of Anatomy, University of Bern, Baltzerstrasse 2 3012 Bern, Switzerland

[3]Department of Genetics, Faculty of Medical Sciences, University of Kragujevac, 69 Svetozar Markovic Street, Kragujevac, Serbia

[4]Department of Microbiology and Immunology, Faculty of Medical Sciences, University of Kragujevac, 69 Svetozar Markovic Street, Kragujevac, Serbia

*Correspondence should be sent to:

Prof. Vladislav Volarevic

e-mail: drvolarevic@yahoo.com ; telephone number/fax number: +38134306800

Postal address: 69 Svetozar Markovic Street, 34000 Kragujevac, Serbia

Abstract

Mesenchymal stem cell (MSC)-dependent biological effects in the tumor microenvironment mainly rely on the activity of MSC-sourced microRNAs (MSC-miRNAs) which modulate protein synthesis in target tumor cells, endothelial cells and tumor-infiltrated immune cells, regulating their phenotype and function. Several MSC-sourced miRNAs (miR-221, miR-23b, miR-21-5p, miR-222/223, miR-15a miR-424, miR-30b, miR-30c) possess tumor-promoting properties and are able to enhance viability, invasiveness and metastatic potential of malignant cells, induce proliferation and sprouting of tumor endothelial cells and suppress effector functions of cytotoxic tumor-infiltrated immune cells, crucially contributing to the rapid growth and progression of tumor tissue. On the contrary, MSCs also produce "anti-tumorigenic" miRNAs (miR-100, miR-222-3p, miR-146b miR-302a, miR-338-5p, miR-100-5p and miR-1246) which suppress tumor growth and progression by: up-regulating expression of chemoresistance-related genes in tumor cells, by suppressing neo-angiogenesis and by inducing generation of tumorotoxic phenotypes in tumor-infiltrated lymphocytes. In this review article, we summarize the current knowledge about molecular mechanisms that are responsible for MSC-miRNA-dependent alterations of intracellular signaling in tumor and immune cells and we discuss different insights regarding the therapeutic potential of MSC-derived miRNAs in cancer treatment.

Keywords: mesenchymal stem cells; microRNAs; tumor; angiogenesis; anti-tumor immunity

Introduction

Mesenchymal stem cells (MSC) are self-renewable, multipotent and immunoregulatory stem cells which reside in almost all postnatal tissues where, through the interaction with parenchymal and immune cells, they regulate cellular homeostasis and promote repair and regeneration of injured tissues (Gazdic et al., 2015). The therapeutic potential of MSCs in tissue regeneration is best exemplified in MSC-dependent wound healing (Harrell et al., 2021a). Large numbers of chemokine receptors are expressed on the membrane of MSCs, enabling their rapid recruitment to the site of injury (Harrell et al., 2021a). Alarmins and damage-associated molecular patterns (DAMPs), which are released from injured parenchymal cells, bind to alarmin/DAMP-specific receptors on tissue-resident macrophages and induce massive production of inflammatory cytokines and chemokines that recruit MSCs from their niches into the site of injury. Upon migrating to the wounds, MSCs integrate into damaged tissues and modulate the viability of injured parenchymal cells, induce differentiation of resident progenitor cells and alter the phenotype and function of tissue-infiltrated immune cells (Harrell et al., 2021a).

Tumors are wounds that never heal (Dvorak, 1986). Accordingly, MSCs are recruited to tumor sites by wound-associated chemokines and inflammatory cytokines produced by tumor-associated macrophages and neutrophils (Harrell et al., 2021b). Within the tumor microenvironment (TME), MSCs regulate viability, growth and invasiveness of malignant cells and modulate the phenotype and function of tumor-infiltrated immune cells (Harrell et al., 2021b). A large number of recently published studies have indicated that MSC-dependent biological effects in TME mainly relied on the activity of MSC-sourced exosomes (MSC-Exos), extracellular vesicles which, due to their lipid envelope and nano-sized dimension, easily by-pass all biological barriers and deliver their cargo directly in target cells (Lin et al., 2022). MSC-Exos contain large number of MSC-sourced microRNAs (MSC-miRNAs) which modulate protein synthesis in target cells through the post-transcriptional regulation of target mRNA (Xu et al., 2020). MSC-miRNAs are small, single-stranded, non-coding RNAs containing 20-22 base sequences. The seed regions (nucleotide sites 2-8)

of MSC-miRNAs bind to the target mRNA and induce its degradation or inhibition of its translational activity (Xu et al., 2020). By binding to the mitochondrial-related mRNA, MSC-miRNAs may modulate mitochondrial function of malignant cells, affecting their viability (Sohrabi et al., 2022). In addition, MSC-miRNAs are able to directly bind to target proteins, altering their function. Also, MSC-miRNAs can bind to other non-coding RNAs, negatively regulating their functions (Xu et al., 2020). Additionally, MSC-miRNAs are able to activate the gene transcription process and to modulate protein synthesis (Sohrabi et al., 2022). MSC-miRNAs may activate toll-like receptor-dependent intracellular signaling cascade in tumor-infiltrated immune cells, enabling enhanced production of inflammatory and anti-tumorigenic cytokines (Sohrabi et al., 2022). Accordingly, a large number of animal studies demonstrated that MSC-miRNAs modulated tumor growth and progression by affecting synthesis of proteins which regulated activation of cell-death-related signaling pathways in tumor cells and which were responsible for the generation of immunosuppressive phenotypes in tumor-infiltrated immune cells (Xu et al., 2020; Harrell et al., 2021b). Additionally, MSC-Exos transfected with synthetic miRNAs managed to significantly enhance the sensitivity of malignant cells to chemotherapeutic drugs and to remarkably improve the efficacy of anti-cancer treatment (Sohrabi et al., 2022). In order to emphasize the role of MSC-miRNAs in tumor growth and progression, in this review article, we summarize current knowledge about molecular mechanisms that are responsible for MSC-miRNA-dependent alterations of intracellular signaling in tumor cells and for MSC-miRNA-based modulation of anti-tumor immunity. An extensive literature review was carried out in February 2023 across several databases (MEDLINE, EMBASE, Google Scholar), from 1990 to present. Keywords used in the selection were: "mesenchymal stem cells", "microRNAs", “signaling pathway”, “tumor”, “viability”, “survival”, “apoptosis”, “cell death”, "angiogenesis", "anti-tumor immunity". All journals were considered and an initial search retrieved 415 articles. The abstracts of all these articles were subsequently reviewed by two of the authors (CRH and VV) independently to check their relevance to the subject of this manuscript. Eligible studies had to delineate molecular and cellular mechanisms responsible

for the MSC-miRNAs-based modulation of tumor growth and progression and their findings were analyzed in this review.

MSC-miRNAs with tumor-promoting capacity

Results obtained in a large number of experimental studies provided evidence that several MSC-miRNAs (miR-221, miR-23b, miR-21-5p, miR-222/223, miR-15a miR-424, miR-30b, miR-30c) possess tumor-promoting properties (Ono et al., 2014; Wang et al., 2014; Ji et al., 2015; Ren et al., 2019; Xu et al., 2019; Luo et al., 2020; Lyu et al., 2021). These "pro-tumorigenic" MSC-miRNAs (i) enhance viability, invasiveness and metastatic potential of malignant cells, (ii) generate a new capillary network within the tumor microenvironment (TME) by inducing proliferation and sprouting of tumor endothelial cells (ECs) and (iii) suppress effector functions of cytotoxic tumor-infiltrated immune cells, crucially contributing to the rapid growth and progression of tumor tissue (Ono et al., 2014; Wang et al., 2014; Ji et al., 2015; Ren et al., 2019; Xu et al., 2019; Luo et al., 2020; Lyu et al., 2021).

As recently emphasized by Zhang and colleagues (Zhang et al., 2022), MSC-sourced miR-221 enhanced proliferative and invasive characteristics of tumor cells by activating Protein kinase B (PKB/AKT), extracellular signal-regulated kinase (ERK)1/2 and c-Jun N-terminal kinase (JNK)-driven signaling cascades in malignant cells. Additionally, Wang and coworkers analyzed the expression of tumor-suppressor genes in MSC-treated HGC-27 gastric cancer cells and demonstrated that MSC-derived miR-221 promoted G_1/S cell cycle transition and significantly increased proliferation of malignant cells by down-regulating expression of tumor-suppressor genes: suppressor of cytokine signaling 1 (SOCS1) and cyclin-dependent kinase inhibitor 1B (CDKN1B) (Wang et al., 2014). Similar to these findings are results obtained by Ren and colleagues who demonstrated that MSC-derived miR-21-5p promotes invasiveness of lung cancer cells. MSC-sourced mR-21-5p increased viability and proliferation of A549 lung cancer cells *in vitro* and enhanced lung cancer growth and progression in MSC-Exo-treated tumor-bearing animals. In

A549 cells, MSC-sourced miR-21-5p attenuated expression of Programmed Cell Death 4 (PDCD4) gene and prevented PDCD4-dependent apoptosis and cell cycle arrest of malignant cells (Ren et al., 2019). Therefore, by delivering miR-21-5p in lung cancer cells, MSC-Exos increased their viability and proliferation, crucially contributing to the rapid growth and progression of lung cancer in MSC-Exo-treated tumor-bearing animals (Ren et al., 2019).

It was recently revealed that MSC-sourced miR-23b, miR-21-5p, miR-222/223 and miR-15a enhanced the resistance of malignant cells to chemotherapy (Ono et al., 2014; Ji et al., 2015; Xu et al., 2019; Luo et al., 2020; Lyu et al., 2021). Ono and colleagues showed that MSC-derived miR-23b induced dormancy and promoted the resistance of BM2 breast cancer cells to docetaxel by suppressing the expression of myristoylated alanine-rich C-kinase substrate (MARCKS) gene which encoded a protein that facilitated cell cycling of BM2 cells (Ono et al., 2014). In line with these results were findings obtained by Luo and colleagues who demonstrated that MSC-sourced miR-21-5p and miR-222/223 promoted the resistance of MDA-MB-231 and T47D breast cancer cells to doxorubicin (DOX) and carboplatin. MSC-derived miR-21-5p and miR-222/223 up-regulated the expression of chemoresistant S100 calcium-binding protein A6 (S100A6) gene and induced G0 cell cycle arrest and dormancy of breast cancer cells (Luo et al., 2020). Similar to these findings were results reported by Zhang and colleagues who demonstrated that MSC-sourced miR-15a induced G0 cell cycle arrest and decreased sensitivity of chronic myeloid leukemia (CML) cells to tyrosine kinase inhibitors (TKIs) (Zhang et al., 2020a). MSC-derived miR-15a increased the viability of CML cells by enhancing synthesis of anti-apoptotic Bcl-2 protein and by suppressing caspase 3-driven apoptosis of TKI-treated CML cells, which significantly increased leukemia progression in experimental animals (Zhang et al., 2020a).

In addition to their direct effects on tumor cells, MSC-miRNAs may promote tumor growth indirectly, by inducing proliferation and sprouting of tumor ECs (Zhang et al., 2022). MSC-sourced miR-424, miR-30b and miR-30c most efficiently increased generation of tube-like structures and induced formation of capillary

network in the TME (Gong et al., 2017). MSC-derived miR-424 induces increased expression of VEGF in tumor cells which, in turn, binds to VEGFR2 on tumor ECs and activates phosphoinositide phospholipase C (PLCγ) and phosphoinositide 3-kinase (PI3K)-driven pathways (Li et al., 2020). PLCγ and PI3K modulate mTOR activity and activate protein kinase C (PKC) and ERK1/2 which suppress caspase-dependent apoptosis and promote cyclin D1 activity in a nuclear factor-κB (NF-κB)-dependent manner, enabling enhanced survival of ECs in the TME (Li et al., 2020). Similar to miR-424, MSC-sourced miR30b and miR30c also enhanced VEGF-dependent sprouting of newly generated blood vessels in the TME. By up-regulating Delta-like 4 (DLL4) gene expression in tumor ECs, MSC-derived miR30b and miR30c induced increased expression of VEGFR on ECs' membranes, enabling neo-vascularization and rapid tumor growth (Bridge et al., 2012).

As recently demonstrated by Ren and colleagues (Ren et al., 2019), MSC-sourced miR-21-5p promoted tumor growth by suppressing macrophage-driven anti-tumor immune response. MSC-derived miR-21-5p down-regulated expression of the Phosphatase and tensin homolog (PTEN) gene which suppressed synthesis of Arginase I and induced alternative activation of tumor-associated macrophages (TAMs). Additionally, MSC-derived miR-21-5p inhibits synthesis of inflammatory cytokines, particularly tumor necrosis factor alpha (TNF-α) and interleukin 1 beta (IL-1β) in TAMs. IL-1β and TNF-α bind to their receptors on tumor ECs and activate MyD88/MAPK-dependent intracellular cascade, resulting in the activation of several transcriptional factors (NF-κB, activator protein 1 (AP-1)) that increase expression of genes responsible for the production of E and P selectins and integrin ligands which facilitate influx of immune cells in the tumor tissue. Accordingly, by inhibiting production of IL-1β and TNF-α in TAMs, MSC-sourced miR-21-5p suppresses TNF-α and IL-1β-dependent recruitment of circulating leukocytes in tumor tissue and attenuates anti-tumor immune response (Ren et al., 2019).

Molecular mechanisms responsible for MSC-miRNAs-dependent tumor suppression

Several recently published studies identified MSC-sourced miRNAs (miR-100, miR-222-3p, miR-146b miR-302a, miR-338-5p, miR-100-5p and miR-1246) with tumor suppressive properties (Pakravan et al., 2017; Li et al., 2019; Zhang et al., 2020b; Yao et al., 2021). These "anti-tumorigenic" MSC-miRNAs either directly affected cell cycle and apoptosis-related pathways in tumor cells or indirectly inhibited tumor growth by preventing neo-angiogenesis and by enhancing anti-tumor immunity.

MSC-derived miR-100, miR-222-3p, miR-146b miR-302a and miR-338-5p suppressed viability, proliferation and invasiveness of malignant cells (Lee et al., 2013; Pakravan et al., 2017; Li et al., 2019; Zhang et al., 2020b; Yao et al., 2021). MSC-sourced miR-100 inhibited mammalian target of rapamycin (mTOR)-dependent hypoxia-inducible factor 1-alpha (HIF1A)-driven cell cycle progression in breast cancer cells and suppressed tumor growth and progression (Pakravan et al., 2017). MSC-derived miR-222-3p targeted interferon regulatory factor 2 (IRF2) gene expression in THP-1 leukemia cells to inhibit IRF2/ inositol polyphosphate-4-phosphatase type II (INPP4B)-dependent proliferation of malignant cells (Zhang et al., 2020b). MSC-sourced miR-146b inhibited glioma expansion in the brains of MSC-Exo-treated rats while MSC-Exo-sourced miR-302a alleviated activating Protein kinase B (PKB/AKT)-dependent expression of cyclin D1 in endometrial cancer cells and reduced endometrial cancer progression (Li et al., 2019). Similarly, MSC-derived miR-338-5p suppressed the Wif1/Wnt8/β-catenin signaling pathway in pancreatic cancer cells and attenuated their proliferation (Yao et al., 2021).

MSC-derived miR-16, miR-100-5p and miR-1246 prevented tumor growth and progression by suppressing generation of capillary network in the TME (Zhang et al., 2022). Lee and colleagues demonstrated that MSC-sourced miR-16 down-regulated VEGF gene expression in murine mammary carcinoma 4T1 cells and alleviated VEGF-dependent neo-angiogenesis of breast cancer (Lee et al., 2013). MSC-Exos did not directly affect viability and proliferation of 4T1 cells but remarkably inhibited their capacity for VEGF production. Importantly, the decreased mRNA level of VEGF in MSC-Exo-treated 4T1 cells was completely restored

when miR-16 inhibitor was added in MSC-Exos, suggesting that MSC-Exo-sourced miR-16 was mainly responsible for down-regulated VEGF expression in MSC-Exo-treated murine breast cancer cells (Lee et al., 2013). MSC-miR16-dependent suppression of VEGF synthesis in 4T1 cells significantly attenuated proliferation and migration of ECs and prevented generation of a capillary network in TME (Lee et al., 2013). Similar to these findings are results obtained by Liu and colleagues who demonstrated that MSC--derived miR-100-5p and miR-1246 reduced vascular density and attenuated growth of oral squamous cell carcinomas in experimental mice by down-regulating expression of VEGF and angiopoietin-1 (Ang1) in tumor ECs (Liu et al., 2022).

It was recently revealed that MSCs are not constitutively immunosuppressive cells and that MSCs may enhance anti-tumor immune response. In line with these findings are results obtained by Li and colleagues who provided evidence about immunostimulatory effects of MSC-miR-182 on tumor-infiltrated immune cells (Li et al., 2021). By using an orthotopic clear cell renal cell carcinoma mouse model they showed that MSC-sourced miR-182 increased proliferation and tumorotoxicity of CD8+ CTLs and NKT cells (Li et al., 2021). MSC-miR182-dependent activation of tumor-infiltrated CTLs and NKT cells resulted in reduced growth and progression of murine renal cancer (Li et al., 2021).

Molecular mechanisms responsible for MSC-miRNA-dependent abrogation of chemoresistance

Considering the fact that miR-122 and miR-199a were able to increase the sensitivity of hepatocellular carcinoma (HCCs) to chemotherapeutic agents (Zhang et al., 2022), Lou and colleagues engineered miR-122 and miR-199a-overexpressing MSCs ($MSC_{miR\text{-}122}$ and $MSC_{miR\text{-}199a}$) which were able to deliver miR-122 and miR-199a-containing Exos directly in HCCs (Lou et al., 2015). $MSC_{miR\text{-}122}$ enhanced 5-fluorouracil (5-FU) and sorafenib-induced apoptosis of HCCs by negatively regulating the expression of miR-122-target genes (cyclin G1, insulin-like growth factor receptor 1, a disintegrin and metalloprotease 10) in HCCs (Lou et al., 2015). Single intra-tumor injection of MSC-$Exos_{miR\text{-}122}$ (given one week after subcutaneous

inoculation of HCCs) significantly up-regulated the expression of apoptosis-related genes (caspase 3 and Bax (Bcl-2 Associated X protein)) and reduced the volume and weight of hepatocellular carcinoma in 5-FU and sorafenib-treated tumor-bearing mice (Lou et al., 2015). Similarly, MSC-sourced miR-199a inhibited the mTOR pathway and sensitized HCC cells to doxorubicin. MSC-miR-199a reduced phosphorylation of eukaryotic translation initiation factor 4E (4EBP1) and phosphoprotein 70 ribosomal protein S6 kinase (70S6K) which decreased mTOR activity and increased sensitivity of HCCs to doxorubicin which significantly reduced growth and progression of hepatocellular carcinoma in doxorubicin-treated tumor-bearing mice (Lou et al., 2015).

In line with these findings are results obtained by Yu and coworkers who showed that $MSC_{miR\text{-}199a}$ suppressed glioma progression by enhancing sensitivity of tumor cells to temozolomide (TMZ) (Yu et al., 2019). $MSC_{miR\text{-}199a}$ increased apoptosis and inhibited the invasive characteristics of TMZ-treated glioma cells *in vitro*. By down-regulating expression of the Arf GTPase-activating protein-2 (AGAP2) gene in glioma cells, $MSC_{miR\text{-}199a}$ inhibited synthesis of AGAP2 protein, prevented AGAP2-dependent elimination of TMZ from glioma cells and increased its cytotoxicity (Yu et al., 2019). Accordingly, $MSC_{miR\text{-}199a}$ significantly reduced glioma growth and progression in TMZ-treated mice, confirming the therapeutic potential of $MSC_{miR\text{-}199a}$ in cancer therapy (Yu et al., 2019). Similarly, MSC-sourced anti-miR-9 and miR-124 abrogated chemoresistance of glioblastoma multiforme (GBM) cells. (Munoz et al, 2013; Sharif et al, 2018). MSC-derived anti-miR-9 weakened TMZ resistance and enhanced TMZ-driven, caspase-dependent apoptosis of GBM cells by suppressing the expression of the drug efflux transporter, P-glycoprotein in GBM cells, (Munoz et al., 2013). MSC-sourced miR-124 attenuated expression of the Cyclin-dependent kinase 6 (CDK6) gene which regulated cell cycle progression, viability and senescence of GBM cells (Sharif et al., 2018). Accordingly, MSC-derived miR-124 significantly increased the chemosensitivity of GBM cells and suppressed their proliferative, migratory and invasive properties (Sharif et al., 2018).

It is well known that miR-193a suppresses non-small cell lung cancer (NSCLC) cell proliferation and

invasiveness by down-regulating expression of epidermal growth factor receptor (Zhang et al., 2022). Based on these findings, Wu and colleagues engineered miR-193a-overexpressing MSCs which produced miR-193-enriched MSC-Exos (MSC-Exos$^{miR-193-a}$) that abrogated resistance of NSCLC cells to cisplatin (DDP) *in vitro* and were able to bypass all biological barriers in the body of lung cancer-bearing animals, enabling optimal delivery of MSC-sourced miR-193a into target NSCLC cells (Wu et al., 2020). Accordingly, combined DDP+ MSC-Exos$^{miR-193-a}$ therapy was more efficient in the suppression of lung cancer growth and progression in experimental animals than DDP-single based treatment, confirming the potential therapeutic use of MSC-Exos$^{miR-193-a}$ in NSCLC lung cancer therapy (Wu et al., 2020).

MSC-sourced miR-221, miR-451, miR-654-3p, miR210-5p, miR-106b-3p, miR-155-5p were able to repair radiation and chemotherapy-induced tissue injury by up-regulating expression of genes that prevent apoptosis, improve viability and enhance proliferation of tumor-neighboring, healthy parenchymal cells (Wen et al., 2016; Kink et al., 2019; Zuo et al., 2019; Zhang et al., 2022). Upon intravenous infusion, MSC-Exos accumulated in the bone marrow of chemotherapy-treated and irradiated tumor bearing animals where, by delivering cell cycle-regulating miR-221, miR-451, miR-654-3p and apoptosis-regulated miR210-5p, miR-106b-3p, miR-155-5p, reversed radiation-induced DNA damage and reduced chemotherapy-induced apoptosis of hematopoietic progenitor cells, crucially contributing to the re-population of leukocytes in the peripheral blood of MSC-Exo-treated experimental animals (Wen et al., 2016).

Conclusions and future perspectives

MSC-Exos are able to selectively deliver their cargo directly in target tumor cells and, because of their biodegradability and low toxicity, have been considered as promising therapeutic carriers of various anti-cancer agents. MSC-Exos may deliver "anti-tumorigenic" MSC-sourced miRNAs (miR-100, miR-222-3p, miR-146b miR-302a, miR-338-5p, miR-100-5p and miR-1246) which are able to suppress tumor growth and progression by: (i) up-regulating expression of chemoresistance-related genes in tumor cells, (ii)

reducing viability and invasiveness of malignant cells, (iii) suppressing neo-angiogenesis in the TME, (iv) inducing generation of tumorotoxic phenotype in CTLs and NKT cells. Although MSC-Exos hold an enormous therapeutic potential in molecular oncology, it should be noted that MSC-Exos also contain "pro-tumorigenic" MSC-derived miRNAs (miR-221, miR-23b, miR-21-5p, miR-222/223, miR-15a miR-424, miR-30b, miR-30c) which enhance the viability, invasiveness and metastatic potential of tumor cells, attenuate chemosensitivity of malignant cells, induce new capillary network formation in the TME and suppress anti-tumor immune response. Therefore, up-coming studies should determine "pro or anti-tumorigenic" potential for all of MSC-sourced miRNAs which are contained within MSC-Exos. Afterwards, MSCs should be bioengineered to produce MSC-Exos with "strict anti-tumorigenic profile" (containing only tumorotoxic and immunostimulatory miRNAs) which could be used in clinical trials as new remedies in cancer treatment without any safety concerns.

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Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

References

Bridge G., Monteiro R., Henderson S., Emuss V., Lagos D., Georgopoulou D., Patient R. and Boshoff C. (2012). The microRNA-30 family targets DLL4 to modulate endothelial cell behavior during angiogenesis. Blood 120, 5063-5072.

Dvorak H.F. (1986). Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing. N. Engl. J. Med. 315, 1650-1659.

Gazdic M., Volarevic V., Arsenijevic N. and Stojkovic M. (2015). Mesenchymal stem cells: a friend or foe in immune-mediated diseases. Stem Cell. Rev. Rep. 11, 280-287.

Gong M., Yu B., Wang J., Wang Y., Liu M., Paul C., Millard R.W., Xiao D.S., Ashraf M. and Xu M. (2017). Mesenchymal stem cells release exosomes that transfer miRNAs to endothelial cells and promote angiogenesis. Oncotarget 8, 45200-45212.

Harrell C.R., Djonov V. and Volarevic V. (2021a). The cross-talk between mesenchymal stem cells and immune cells in tissue repair and regeneration. Int. J. Mol. Sci. 22, 2472.

Harrell C.R., Volarevic A., Djonov VG., Jovicic N. and Volarevic V (2021b). Mesenchymal stem cell: A friend or foe in anti-tumor immunity. Int. J. Mol. Sci. 22, 12429.

Ji R., Zhang B., Zhang X., Xue J., Yuan X., Yan Y., Wang M., Zhu W., Qian H. and Xu W. (2015). Exosomes derived from human mesenchymal stem cells confer drug resistance in gastric cancer. Cell Cycle. 14, 2473-2483.

Lee J.K., Park S.R., Jung B.K., Jeon Y.K., Lee Y.S., Kim M.K., Kim Y.G., Jang J.Y. and Kim C.W. (2013). Exosomes derived from mesenchymal stem cells suppress angiogenesis by down-regulating VEGF expression in breast cancer cells. PLoS One 8, e84256.

Li D., Lin F., Li G. and Zeng F. (2021). Exosomes derived from mesenchymal stem cells curbs the progression of clear cell renal cell carcinoma through T-cell immune response. Cytotechnology 73, 593-604.

Li X., Liu L.L., Yao J.L., Wang K. and Ai H. (2019). Human umbilical cord mesenchymal stem cell-derived extracellular vesicles inhibit endometrial cancer cell proliferation and migration through delivery of exogenous miR-302a. Stem Cell. Inter. 2019, 8108576.

Li S., Wu Y., Zhang J., Sun H. and Wang X. (2020). Role of miRNA-424 in cancers. OncoTargets Ther. 13, 9611-9622.

Lin Z., Wu Y., Xu Y., Li G., Li Z. and Liu T. (2022). Mesenchymal stem cell-derived exosomes in cancer therapy resistance: recent advances and therapeutic potential. Mol. Cancer 21, 179.

Lou G., Song X., Yang F., Wu S., Wang J., Chen Z. and Liu Y. (2015). Exosomes derived from miR-122-modified adipose tissue-derived MSCs increase chemosensitivity of hepatocellular carcinoma. J. Hem. Oncol. 8, 122.

Luo T., Liu Q., Tan A., Duan L., Jia Y., Nong L., Tang J., Zhou W., Xie W., Lu Y., Yu Q. and Liu Y. (2020). Mesenchymal stem cell-secreted exosome promotes chemoresistance in breast cancer via enhancing miR-21-5p-mediated *S100A6* expression. Mol. Ther. Oncol. 19, 283-293.

Lyu T., Wang Y., Li D., Yang H., Qin B., Zhang W., Li Z., Cheng C., Zhang B., Guo R. and Song Y. (2021). Exosomes from BM-MSCs promote acute myeloid leukemia cell proliferation, invasion and chemoresistance via upregulation of S100A4. Exp. Hem. Onc. 10, 24.

Munoz J.L., Bliss S.A., Greco S.J., Ramkissoon S.H., Ligon K.L. and Rameshwar P. (2013). Delivery of functional anti-miR-9 by mesenchymal stem cell-derived exosomes to glioblastoma multiforme cells conferred chemosensitivity. Mol. Ther. Nucleic Acids. 2, e126.

Ono M., Kosaka N., Tominaga N., Yoshioka Y., Takeshita F., Takahashi R.U., Yoshida M., Tsuda H., Tamura K. and Ochiya T. (2014). Exosomes from bone marrow mesenchymal stem cells contain a microRNA that promotes dormancy in metastatic breast cancer cells. Sci. Signal. 7, 63.

Pakravan K., Babashah S., Sadeghizadeh M., Mowla S.J., Mossahebi-Mohammadi M., Ataei F., Dana N. and Javan M. (2017). MicroRNA-100 shuttled by mesenchymal stem cell-derived exosomes suppresses

in vitro angiogenesis through modulating the mTOR/HIF-1α/VEGF signaling axis in breast cancer cells. Cell. Oncol. 40, 457-470.

Ren W., Hou J., Yang C., Wang H., Wu S., Wu Y., Zhao X. and Lu C. (2019). Extracellular vesicles secreted by hypoxia pre-challenged mesenchymal stem cells promote non-small cell lung cancer cell growth and mobility as well as macrophage M2 polarization via miR-21-5p delivery. J. Exp. Clin. Res. 38, 62.

Sharif S., Ghahremani M.H. and Soleimani M. (2018). Delivery of exogenous miR-124 to glioblastoma multiform cells by Wharton's Jelly mesenchymal stem cells decreases cell proliferation and migration, and confers chemosensitivity. Stem Cell. Rev. Rep. 14, 236-246.

Sohrabi B., Dayeri B., Zahedi E., Khoshbakht S., Nezamabadi P.N., Ranjbar H., Davari N.A., Noureddini M. and Alani B. (2022). Mesenchymal stem cell (MSC)-derived exosomes as novel vehicles for delivery of miRNAs in cancer therapy. Cancer Gene Ther. 29, 1105-1116.

Yu L., Gui S., Liu Y., Qiu X., Zhang G., Zhang X., Pan J., Fan J., Qi S. and Qiu B. (2019). Exosomes derived from microRNA-199a-overexpressing mesenchymal stem cells inhibit glioma progression by down-regulating AGAP2. Aging (Albany NY). 11, 5300-5318.

Volarevic V., Gazdic M., Simovic Markovic B., Jovicic N., Djonov V. and Arsenijevic N. (2017). Mesenchymal stem cell-derived factors: Immuno-modulatory effects and therapeutic potential. Biofactors 43, 633-644.

Wang M., Zhao C., Shi H., Zhang B., Zhang L., Zhang X., Wang S., Wu X., Yang T., Huang F., Cai J., Zhu Q., Zhu W., Qian H. and Xu W. (2014). Deregulated microRNAs in gastric cancer tissue-derived mesenchymal stem cells: novel biomarkers and a mechanism for gastric cancer. Brit. J. Cancer. 110, 1199-210.

Wen S., Dooner M., Cheng Y., Papa E., Del Tatto M., Pereira M., Deng Y., Goldberg L., Aliotta J., Chatterjee D., Stewart C., Carpanetto A., Collino F., Bruno S., Camussi G. and Quesenberry P. (2016).

Mesenchymal stromal cell-derived extracellular vesicles rescue radiation damage to murine marrow hematopoietic cells. Leukemia 30, 2221-2231.

Wu H., Mu X., Liu L., Wu H., Hu X., Chen L., Liu J., Mu Y., Yuan F., Liu W. and Zhao Y. (2020). Bone marrow mesenchymal stem cells-derived exosomal microRNA-193a reduces cisplatin resistance of non-small cell lung cancer cells via targeting LRRC1. Cell Death Dis. 11, 801.

Xu H.K., Chen L.J., Zhou S.N., Li Y.F. and Xiang C. (2020). Multifunctional role of microRNAs in mesenchymal stem cell-derived exosomes in treatment of diseases. World J. Stem Cells 12, 1276-1294.

Xu H., Han H., Song S., Yi N., Qian C., Qiu Y., Zhou W., Hong Y., Zhuang W., Li Z., Li B. and Zhuang W. (2019). Exosome-transmitted PSMA3 and PSMA3-AS1 promote proteasome inhibitor resistance in multiple myeloma. Clin. Cancer Res. 25, 1923-1935.

Zhang F., Lu Y., Wang M., Zhu J., Li J., Zhang P., Yuan Y. and Zhu F. (2020a). Exosomes derived from human bone marrow mesenchymal stem cells transfer miR-222-3p to suppress acute myeloid leukemia cell proliferation by targeting IRF2/INPP4B. Mol. Cell. Prob. 51, 101513.

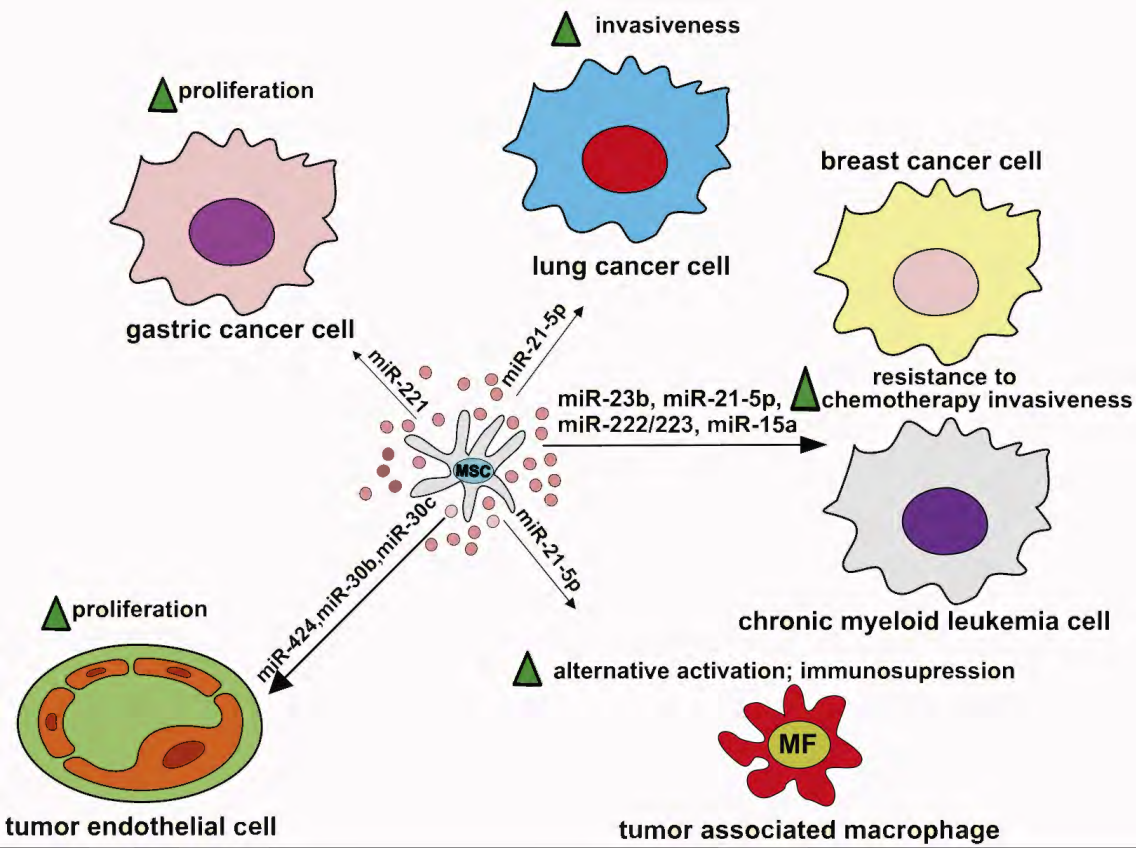
Zhang X., Yang Y., Yang Y., Chen H., Tu H. and Li J. (2020b). Exosomes from bone marrow microenvironment-derived mesenchymal stem cells affect CML cells growth and promote drug resistance to tyrosine kinase inhibitors. Stem Cell. Inter. 2020, 8890201.

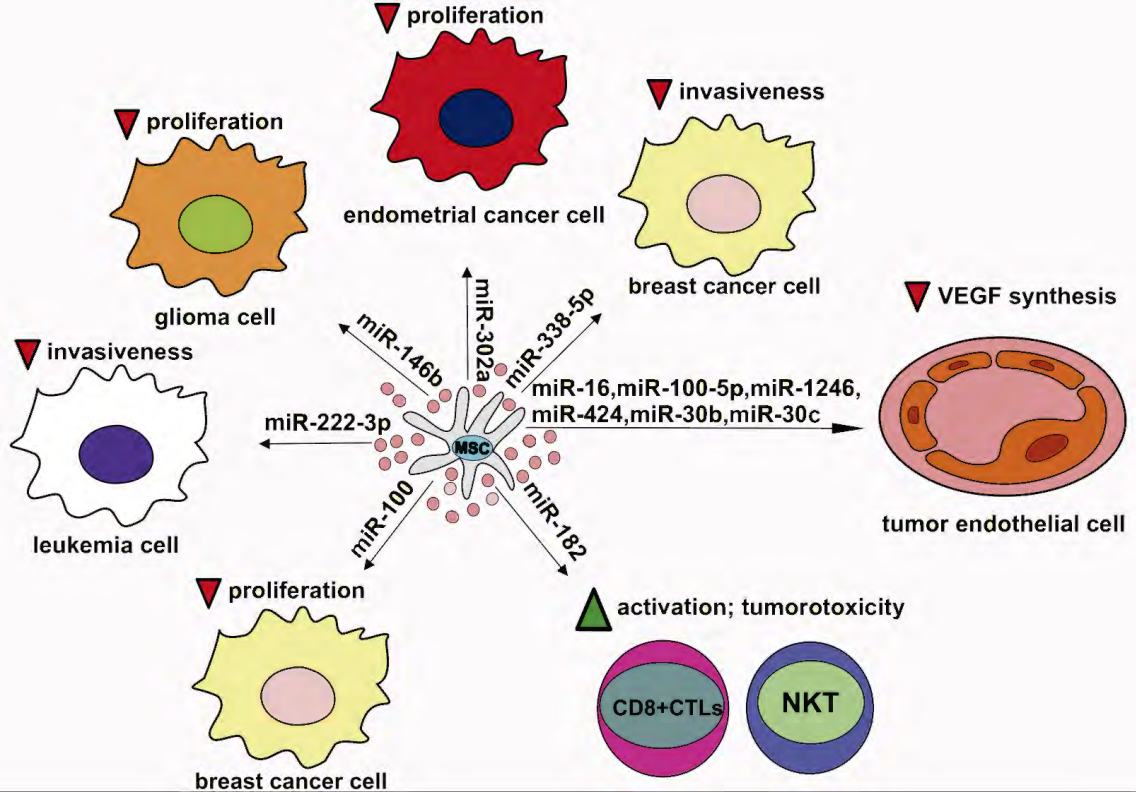
Zhang F., Guo J., Zhang Z., Qian Y., Wang G., Duan M., Zhao H., Yang Z. and Jiang X. (2022). Mesenchymal stem cell-derived exosome: A tumor regulator and carrier for targeted tumor therapy. Cancer Lett. 526, 29-40.

Figure and figure legends

Figure 1. MSC-derived miRNAs which promote tumor growth and progression. MSC-sourced miR-221 and miR-21-5p increase proliferation of gastric and lung cancer cells, respectively. MSC-derived miR-23b, miR-21-5p, miR-222/223, miR-15a increase chemoresistance of breast cancer cells and chronic myeloid leukemia cells. MSC-sourced miR-424, miR-30b, miR-30c increase proliferation and sprouting of tumor endothelial cells. MSC-derived miR-21-5p induces alternative activation of tumor associated macrophages and induces suppression of anti-tumor immunity.

Figure 2. MSC-sourced miRNAs with anti-tumorigenic properties. MSC-sourced miR-100, miR-222-3p miR-146b, miR-302a, miR-338-5p suppress proliferation and invasiveness of breast cancer, leukemia, glioma, endometrial cancer cells, respectively. MSC-derived miR-16, miR-100-5p, miR-1246 miR-424, miR-30b, miR-30c suppress synthesis of vascular endothelial grpwth factor (VEGF) and attenuate neo-angiogenesis in the tumor microenvironment. MSC-sourced miR-182 enhances activation and proliferation of cytotoxic CD8+ T lymphocytes (CTLs) and natural killer T (NKT) cells.


invasiveness
proliferation
lung cancer cell
breast cancer cell
gastric cancer cell
miR-221
miR-21-5p
miR-23b, miR-21-5p,
miR-222/223, miR-15a
resistance to
chemotherapy invasiveness
MSC
miR-21-5p
chronic myeloid leukemia cell
proliferation
miR-424,miR-30b,miR-30c
alternative activation; immunosupression
MF
tumor endothelial cell
tumor associated macrophage


proliferation
endometrial cancer cell
proliferation
glioma cell
invasiveness
breast cancer cell
VEGF synthesis
invasiveness
leukemia cell
miR-302a
miR-146b
miR-338-5p
miR-222-3p
MSC
miR-16,miR-100-5p,miR-1246,
miR-424,miR-30b,miR-30c
tumor endothelial cell
miR-100
miR-182
proliferation
breast cancer cell
activation; tumorotoxicity
CD8+CTLs
NKT