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Popular Article

The Therapeutic Potential of Stem Cell-derived Exosomes

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Abstract

Exosomes, which are small vesicles measuring 30 to 200 nm and showcasing molecular diversity, are derived from mesenchymal stem cells (MSCs) and serve pivotal functions in intercellular communication. MSC-derived exosomes, contains proteins, lipids, nucleic acids, and glycoconjugates, and has intrinsic implications in cancer, inflammatory diseases, and cardio-protection. There are also therapeutic applications of MSC-derived exosomes in diverse medical realms, because of their immunomodulatory properties and anti-inflammatory effects in conditions such as cardiovascular, renal, pulmonary, dermatological, and neurological diseases. The evolving landscape of regenerative medicine positions MSC-derived exosomes as promising tools, although further research is needed to understand the intricate mechanisms underlying their therapeutic effects and optimize their clinical application.

Keywords: Exosomes, Mesenchymal stem cells, Intercellular communication, Therapeutic applications

Introduction

Exosomes, small single-membrane organelles ranging from 30 to 200 nm, boast a cellular topology and are marked by an enrichment in specific proteins, lipids, nucleic acids, and glycoconjugates(Yu et al., 2024). With notable molecular heterogeneity, these vesicles form through budding processes at both plasma and endosome membranes, serving as a mechanism for maintaining protein quality control in exosome biogenesis. Upon release, exosomes embark on a myriad of activities, including remodelling the extracellular matrix and

transmitting signals and molecules to neighbouring cells. This intercellular vesicle traffic pathway plays pivotal roles in diverse aspects of human health and disease, spanning development, immunity, tissue homeostasis, cancer, and neurodegenerative diseases(Simeone et al., 2020). Intriguingly, viruses exploit exosome biogenesis pathways to assemble infectious particles and establish host permissiveness.

Simultaneously, MSC, a diverse subset of multipotent precursors found in various tissues, exhibit the remarkable capacity to differentiate into multiple cell types. Beyond their self-renewal ability through numerous cell divisions, MSC display anti-inflammatory and immunosuppressive properties through direct interactions with immune cells. Recent attention has surged towards the MSC secretome, encompassing cytokines, chemokines, growth factors, and extracellular vesicles (EV). Within the realm of EV, ectosomes and exosomes emerge as two distinct subtypes. Ectosomes, ranging from 50 nm to 1 µm, result from direct budding with the plasma membrane(Fonseka et al., 2021). Conversely, exosomes, sized from 40 to 160 nm, originate from endosomal compartments and are prevalent in bodily fluids. These exosomes, defined by a lipid bilayer membrane, encapsulate a comprehensive array of molecular constituents, including DNA, RNA, lipids, and proteins.Exhibiting unique capabilities, exosomes influence various activities through the exchange of bioactive components with neighbouring cells, transporting genetic contents to distant cell subpopulations that likely mirror the molecular and genetic profiles of the parent cells. Remarkably, MSC-derived exosomes emerge as potent therapeutic agents, showcasing a broad spectrum of therapeutic effects analogous to those attributed to MSC themselves.

Contents of Mesenchymal Stem Cell-derived Exosomes

Exosomes associated with plasma membranes comprise a variety of lipids, including hexosylceramides, cholesterol, phosphatidylserine, sphingomyelin, and saturated fatty acids. Additionally, these vesicles are enriched in proteins with diverse functions, encompassing those associated with exosome biogenesis (e.g., ESCRT complex, ALIX, TSG101, and syntenin), membrane transporters, and fusion proteins (e.g., Rab GTPases and annexins). During exosome biogenesis, an evolutionarily conserved set of proteins is packaged, including tetraspanins (e.g., CD9, CD63, CD81, and CD82), integrins, major histocompatibility complex (MHC) class II proteins, and heat shock proteins(Hu et al., 2020).

Exosomes exhibit diversity reflective of the original cell types and play a crucial role in determining cellular function. Specifically, exosomes derived from MSC express common surface markers such as CD81 and CD9, along with MSC characteristic markers CD73, CD44,

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and CD90(L. Ramos et al., 2016). Proteomic analysis of exosomes derived from bone marrow mesenchymal stem cells (BMSC) identified 730 functional proteins, including those controlling cell growth, proliferation, adhesion, migration, and morphogenesis capacities of MSC. Comprehensive proteomic analysis of human primed MSC-secreted exosomes revealed higher fractions of specific extracellular-associated proteins compared to their cells of origin. These findings contribute to understanding the distinct functional properties of MSC-derived exosomes, including their ability to induce mitosis and potentiate growth factor secretions. In addition to specific proteins, exosomes contain a substantial amount of RNA, forming a significant portion of their contents. The packaging of RNA into exosomes is not random but rather specific, indicating a preferential accumulation of certain RNA molecules. This suggests the existence of a unique "zipcode" sequence, particularly evident in the abundant specific mRNA found in exosomes, which can ultimately be incorporated into recipient cells(Xunian & Kalluri, 2020). In the context of MSC-derived exosomes, the enclosed RNA plays roles in regulating cell survival, differentiation, and immune system modulation.

A comprehensive examination of microRNA (miRNA) in MSC-derived exosomes identified the top 23 miRNA capable of promoting angiogenesis, tissue remodelling, and cardiomyocyte proliferation. Comparing the complete RNA content between bone marrow MSC (BMSC) and adipose-MSC (AMSC)-derived exosomes revealed similarities in RNA composition but striking differences in tRNA species associated with the MSC differentiation status(Ferguson et al., 2018).Beyond proteins and RNA, various types of DNA have been identified in exosomes. Previous studies detected large fragments of double-stranded DNA (dsDNA), indicating the potential for detecting mutations in KRAS and p53 for pancreatic cancer prediction using genomic DNA from exosome DNA(Kahlert et al., 2014). The transfer of exosome DNA into target cells has been reported to exert multiple biological activities transiently. Tumour-derived exosomes, for instance, contain immunostimulatory DNA recognised by cytoplasmic DNA receptors in activated dendritic cells, inducing the STING-dependent pathway and driving anti-tumour immunity. Horizontal DNA gene transfer by exosomes released from BMSC has been observed, carrying high-molecular DNA primarily associated with the outer exosome membrane, facilitating the exchange of genetic information in intercellular communication during cell evolution and development. Additionally, exosomes have the capability to package and transfer their mitochondrial DNA to breast cancer cells, resulting in the restoration of metabolic activity and increased self-renewal potential.

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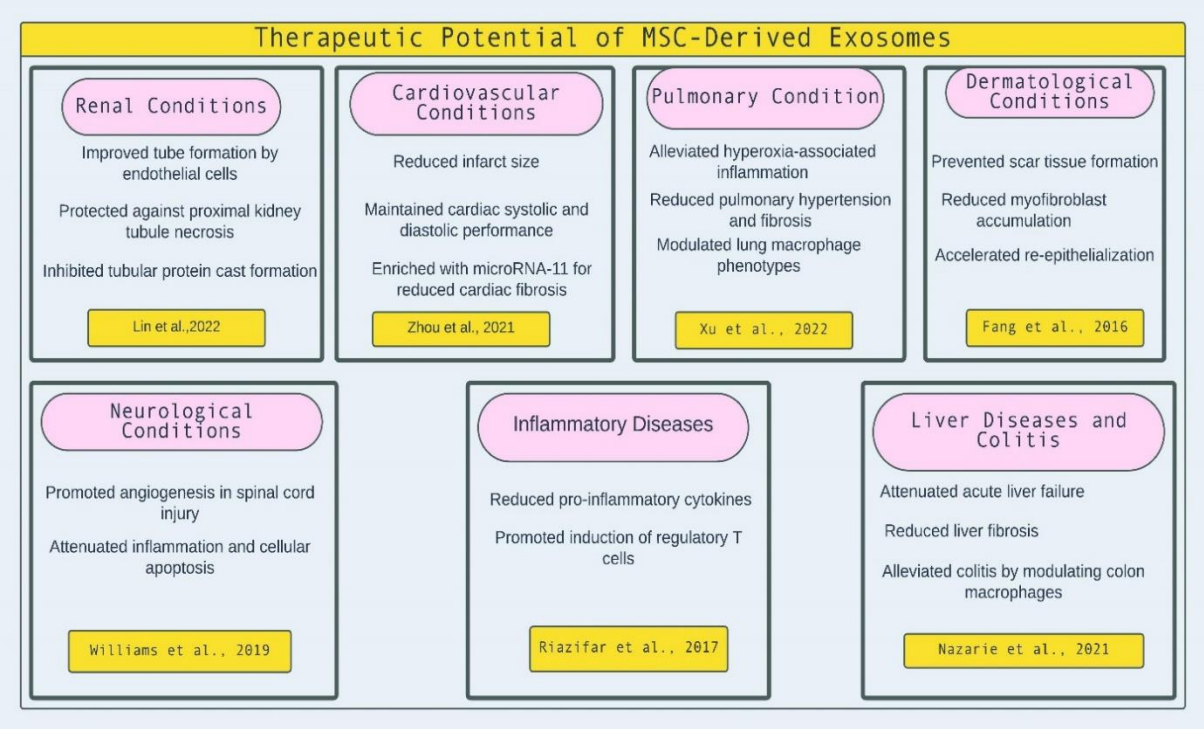
Functions of Mesenchymal Stem Cell-derived Exosomes in Cancer

Accumulating evidence has established a connection between the transfer of tumour-associated miRNA enriched in MSC-derived exosomes and the modulation of cancer cell proliferation, either promoting or inhibiting it. The role of BMSC-derived exosomes, for example, has been extensively studied. Enriched miR-222-3p in these exosomes was found to directly target IRF2, negatively regulating IRF2/INPP4B signalling and suppressing tumour growth in acute myeloid leukaemia (AML) cells. Additionally, exosomes delivered miR101-3p, inhibiting oral cancer progression by targeting COL10A1(Jahangiri et al., 2023).

Not only BMSC-derived exosomes but also those from human umbilical cord mesenchymal stem cells (hUCMSC) demonstrated tumoricidal properties. They inhibited the growth of human lymphoma cells and prostate cancer cells through various mechanisms, such as cell cycle blocking, induction of antioxidant activity, and apoptosis(Damasceno et al., 2020). Conversely, some studies reported a tumor-promoting effect, with BMSC-derived exosomes activating extracellular signal-regulated kinase 1/2 (ERK1/2) signalling in gastric cancer and facilitating multiple myeloma progression by transferring tumour suppressor miR-15a(Aldoghachi et al., 2023).



The role of exosomes in angiogenesis is complex. BMSC-derived exosomes, through various miRNAs and Wnt signalling, were shown to enhance angiogenesis, promoting tumour growth(Lu et al., 2020). On the contrary, BMSC-derived exosomes targeted hypoxia-inducible factor-1 alpha (HIF-1α) and Smad2, inhibiting angiogenesis. The contradictory effects extend

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to anti-vascular remodelling, where exosomal miR-16 and miR-100 demonstrated anti-angiogenic properties in breast cancer cells(Xunian & Kalluri, 2020).

Metastasis, the outgrowth of tumour cells to distant locations, is influenced by exosomes in the tumour microenvironment (TME). BMSC-derived exosomes were found to influence cancer metastasis positively and negatively. They suppressed breast cancer cell metastasis by shuttling miR-205 and miR-31, while also promoting cycling quiescence and early breast cancer dormancy through miR-222/223 transfer(Tomar et al., 2020). Similarly, exosomes from AMSC were involved in both promoting and inhibiting breast cancer cell migration and metastasis.Exosomes play a role in drug resistance, influencing the response to therapeutic treatments. BMSC-derived exosomes were implicated in bortezomib resistance in multiple myeloma cells, and hUCMSC-derived exosomes conferred resistance to 5-fluorouracil (5-Fu) in gastric cancer by inducing multidrug resistance-associated proteins and activating MAPK and Raf/MEK/ERK kinase signalling(Lin et al., 2022). These findings highlight the diverse and intricate roles of exosomes in cancer biology.

Mesenchymal Stem Cell-Derived Exosomes as New Remedies in the Therapy of Inflammatory Diseases

MSC-derived exosomes have proven effective in treating various disease models. In a rat myocardial infarction (MI) model, Teng et al. observed substantial improvements facilitated by MSC-derived exosomes, including enhanced tube formation by endothelial cells, impaired T cell functions, reduced infarct size, and maintained cardiac systolic and diastolic performance. Additionally, exosomes enriched with microRNA (miR)-11, obtained through ischaemic pre-conditioning, significantly reduced infarct size and cardiac fibrosis in a mouse post-myocardial infarction model(Lin et al., 2022). In a cisplatin-induced acute kidney injury model, exosomes from human umbilical cord-derived MSCs, as described by Zhou et al., effectively mitigated blood urea nitrogen and creatinine levels, proximal kidney tubule necrosis, and tubular protein cast formation through anti-oxidative and anti-apoptotic mechanisms(Birtwistle et al., 2021). Addressing pulmonary conditions, MSC-derived exosomes alleviated hyperoxia-associated inflammation, bronchopulmonary dysplasia, pulmonary hypertension, fibrosis, and pulmonary vascular remodelling by modulating lung macrophage phenotypes in a preclinical model(Xu et al., 2022).

Cho et al. demonstrated therapeutic effects of exosomes from human adipose tissue-derived MSCs in allergic conditions. In a mouse model of atopic dermatitis, these exosomes reduced IgE levels, eosinophils, infiltrated mast cells, and CD86+ and CD206+ cells(Cho et

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al., 2018). In wound healing, umbilical cord MSC-derived exosomes prevented scar tissue formation and reduced myofibroblast accumulation through inhibition of the TGF-β/SMAD2 pathway in a skin-defect mouse model(Fang et al., 2016). These exosomes also accelerated re-epithelialisation with increased expression of CK19, PCNA, and collagen I in vivo. In muscle tissue, MSC-derived exosomes promoted regeneration by enhancing myogenesis and angiogenesis, with miR-494 implicated in the muscle regeneration process(Nikfarjam et al., 2020).

In autoimmune conditions, Riazifar et al. demonstrated that MSC-derived exosomes reduced pro-inflammatory cytokine levels and promoted the induction of regulatory T cells (Tregs) in an experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis(Riazifar, 2017). Furthermore, exosome treatment holds promise for neural injuries and neurodegenerative diseases. In a traumatic brain injury (TBI) model, exosomes enhanced functional recovery, increased neuroplasticity, and exhibited neuroprotective effects. In spinal cord injury-related studies, exosomes promoted angiogenesis, hindlimb locomotor activity, tissue sparing, and attenuated inflammation and cellular apoptosis(Williams et al., 2019). In Alzheimer's disease, MSC-derived exosomes stimulated neurogenesis, moderated beta-amyloid-induced cognitive impairment, and ameliorated cognitive decline by rescuing synaptic dysfunction and regulating inflammatory responses(Nakano et al., 2020).

Recent studies emphasise the significant impact of mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) on alleviating colitis, with a focus on modulating colon macrophages.MSC-EVs attenuated the concentration of macrophage-sourced inflammatory cytokines and chemokines, as well as Th1-derived IFN-γ in the gut. This was accompanied by an increase in immunosuppressive cytokines (IL-10 and TGF-β), promoting repair and regeneration of DSS-injured epithelial cells(Barnhoorn et al., 2020).

In the context of liver diseases, MSC-derived secretome and EVs show efficacy in attenuating acute liver failure and liver fibrosis in mice. These effects are achieved by suppressing major effector cells, such as natural killer T (NKT) cells in acute liver failure and CD4+ T helper lymphocytes and hepatic stellate cells (HSCs) in liver fibrosis. MSC-EVs contain high concentrations of NO and reactive nitrogen species, reducing the proliferation of liver NKT cells and protecting hepatocytes from apoptosis. Additionally, MSC-EVs promote hepatocyte proliferation through sphingosine kinase 1 (SK1)/sphingosine-1-phosphate (S1P) signalling(Nazarie et al., 2021).

In chronic liver inflammation and fibrosis, MSC-EVs target liver macrophages

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(Kupffer cells) to suppress inflammatory cytokines and pro-fibrotic TGF-β1. HSCs are also influenced by MSC-EVs, leading to reduced fibrosis through the regulation of autophagy-related proteins and the down-regulation of pro-fibrotic genes. The modulation of macrophage and HSC function contributes to the overall anti-inflammatory and anti-fibrotic effects of MSC-EVs in liver diseases(Chiabotto et al., 2020).

These discoveries collectively underscore the diverse immunomodulatory properties of MSC-EVs across various inflammatory diseases, positioning them as promising candidates for next-generation therapeutics. The ability of MSC-EVs to regulate immune cell function, mitigate inflammation, and promote tissue repair highlights their potential in addressing a wide array of inflammatory conditions. However, further research is essential to unravel the intricate mechanisms underlying these therapeutic effects and optimise the utilisation of MSC-EVs in clinical settings.

MSC-EVs on cardio-protection

In the domain of cardio-protection, a plethora of studies have demonstrated the efficacy of MSC-EVs in safeguarding cardiomyocytes from ischaemic injury. In an animal model of I/R-induced myocardial injury, Lai and colleagues observed that Exos from human embryonic stem cell-derived MSCs significantly reduced infarct size and improved cardiac function(Yue et al., 2022). MSC-Exos exerted their effects by attenuating oxidative stress in I/R-injured hearts, as evidenced by increased tissue levels of ATP and nicotine adenine dinucleotide, along with decreased levels of reactive oxygen species. The presence of Parkinson protein 7/DJ-1 (DJ-1) in MSC-Exos contributed to the modulation of oxidative balance in ischaemic hearts. MSC-Exos containing DJ-1 may be explored further for their potential in promoting cardiac regeneration after ischaemic injury. The cardioprotective effects of MSC-Exos were also associated with increased phosphorylation and activation of kinases (Akt and Glycogen synthase kinase 3 (GSK3)), preventing apoptosis in injured cardiomyocytes, and the suppression of c-Jun-N-terminal kinase, which promotes apoptosis in ischaemic hearts(Yue et al., 2022).

Akt kinase emerged as a crucial intracellular target for MSC-EV-based cardio-protection, as demonstrated by Yu and colleagues. Exos from Gata-4-overexpressing bone marrow-derived MSCs significantly reduced the size of ischaemic lesions and restored cardiac function in a rat model of acute myocardial infarction (AMI) by activating the Akt-dependent signalling pathway in injured cardiomyocytes(Yue et al., 2022). Among the numerous miRNAs present in MSC-Exos, miR-19a played a central role in inducing anti-apoptotic effects in

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ischaemic hearts. MSC-sourced miR-19a down-regulated the activation of PTEN, promoting the phosphorylation and activation of Akt, resulting in the up-regulation of the anti-apoptotic Bcl-2 protein and reducing apoptotic loss of cardiomyocytes. Similarly, Exos from endometrium-derived MSCs improved the recovery of cardiac function after AMI by promoting Akt-dependent up-regulation of Bcl-2 activity in injured cardiomyocytes. The involvement of MSC-derived miR-21 in the cardioprotective effects was highlighted, with miR-21-containing MSC-Exos inducing enhanced expression of vascular endothelial growth factor (VEGF) and promoting neovascularisation in ischaemic hearts, significantly improving cardiac function after AMI.The delivery of miR-22 via MSC-Exos into ischaemic cardiomyocytes was primarily responsible for the observed improvement in cardiac function in mice with AMI(Wang et al., 2021). The reduced infarct size and cardiac fibrosis were attributed to the miR-22-dependent down-regulation of methyl-CpG-binding protein 2, an epigenetic regulator that was up-regulated in ischaemic hearts. Importantly, MSC-EVs not only exhibited anti-apoptotic effects but also suppressed the influx of circulating leukocytes in injured hearts, contributing to the attenuation of ongoing inflammation. The reduced release of alarmins and damage-associated molecular patterns (DAMPs) from MSC-EV-treated cardiomyocytes led to a decreased secretion of leukocyte-attracting chemokines by resident macrophages. Consequently, after reperfusion, a significantly lower number of neutrophils, monocytes, and lymphocytes infiltrated the myocardium of MSC-Exo-treated animals, indicating that the suppression of the inflammatory response by MSC-Exos also played a role in enhancing the repair and regeneration of injured cardiomyocytes(Ozaki Tan et al., 2020).

Conclusion

In conclusion, the intricate world of exosomes derived from MSCs presents a dynamic landscape of potential therapeutic applications across diverse medical realms. These small vesicles, rich in proteins, lipids, nucleic acids, and glycoconjugates, play pivotal roles in intercellular communication and exhibit remarkable heterogeneity reflective of their cellular origins. In the context of cancer, MSC-derived exosomes showcase dualistic roles, influencing tumour growth, angiogenesis, metastasis, and drug resistance. Meanwhile, their immunomodulatory properties position them as promising agents in the treatment of inflammatory diseases, spanning cardiovascular, renal, pulmonary, dermatological, and neurological conditions. Moreover, these exosomes hold significant potential in addressing liver diseases, offering anti-inflammatory and anti-fibrotic effects.The therapeutic potential of MSC-derived exosomes extends to cardio-protection, where they demonstrate efficacy in

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safeguarding cardiomyocytes from ischaemic injury through modulation of oxidative stress, activation of kinases, and regulation of apoptotic pathways. The delivery of specific microRNAs via exosomes emerges as a key mechanism underlying their cardioprotective effects. In the evolving landscape of regenerative medicine, MSC-derived exosomes emerge as powerful tools, exerting multifaceted influences on cellular function, tissue repair, and immune responses. However, while the potential is vast, further research is essential to unravel the intricate mechanisms underlying these effects and optimise their application in clinical settings. The journey of MSC-derived exosomes from cellular communication agents to therapeutic powerhouses represents a promising frontier in the ongoing quest for innovative medical interventions.

References

Aldoghachi, A. F., Chong, Z. X., Yeap, S. K., Cheong, S. K., Ho, W. Y., & Ong, A. H. K. (2023). Stem cells for cancer therapy: Translating the uncertainties and possibilities of stem cell properties into opportunities for effective cancer therapy. *International Journal of Molecular Sciences*, *24*(2), 1012. https://doi.org/10.3390/ijms24021012

Barnhoorn, M. C., Plug, L., Jonge, E. S. M. M., Molenkamp, D., Bos, E., Schoonderwoerd, M. J. A., Corver, W. E., van der Meulen-De Jong, A. E., Verspaget, H. W., & Hawinkels, L. J. A. C. (2020). Mesenchymal stromal cell–derived exosomes contribute to epithelial regeneration in experimental inflammatory bowel disease. *Cellular and Molecular Gastroenterology and Hepatology*, *9*(4), 715–717.e8. https://doi.org/10.1016/j.jcmgh.2020.01.007

Birtwistle, L., Chen, X.-M., & Pollock, C. (2021). Mesenchymal stem cell-derived extracellular vesicles to the rescue of renal injury. *International Journal of Molecular Sciences*, *22*(12), 6596.

Chiabotto, G., Pasquino, C., Camussi, G., & Bruno, S. (2020). Molecular pathways modulated by mesenchymal stromal cells and their extracellular vesicles in experimental models of liver fibrosis. *Frontiers in Cell and Developmental Biology*, *8*, 594794. https://doi.org/10.3389/fcell.2020.594794

Cho, B. S., Kim, J. O., Ha, D. H., & Yi, Y. W. (2018). Exosomes derived from human adipose tissue-derived mesenchymal stem cells alleviate atopic dermatitis. *Stem Cell Research and Therapy*, *9*(1), 187. https://doi.org/10.1186/s13287-018-0939-5

Damasceno, P. K. F., De Santana, T. A., Santos, G. C., Orge, I. D., Silva, D. N., Albuquerque, J. F., Golinelli, G., Grisendi, G., Pinelli, M., Ribeiro dos Santos, R., Dominici, M., & Soares, M. B. P. (2020). Genetic engineering as a strategy to improve the therapeutic efficacy of mesenchymal stem/stromal cells in regenerative medicine. *Frontiers in Cell and Developmental Biology*, *8*, 737. https://doi.org/10.3389/fcell.2020.00737

Fang, S., Xu, C., Zhang, Y., Xue, C., Yang, C., Bi, H., Qian, X., Wu, M., Ji, K., Zhao, Y., Wang, Y., Liu, H., & Xing, X. (2016). Umbilical cord-derived mesenchymal stem cell-derived exosomal microRNAs suppress myofibroblast differentiation by inhibiting the transforming growth factor-β/SMAD2 pathway during wound healing. *Stem Cells Translational Medicine*, *5*(10), 1425–1439. https://doi.org/10.5966/sctm.2015-0367

Ferguson, S. W., Wang, J., Lee, C. J., Liu, M., Neelamegham, S., Canty, J. M., & Nguyen, J. (2018). The microRNA regulatory landscape of MSC-derived exosomes: A systems view. *Scientific Reports*, *8*(1), 1419. https://doi.org/10.1038/s41598-018-19581-x

Fonseka, P., Marzan, A. L., & Mathivanan, S. (2021). Introduction to the community of extracellular vesicles. *Sub-Cellular Biochemistry* (pp. 3–18). https://doi.org/10.1007/978-3-030-67171-6_1

Hu, Q., Su, H., Li, J., Lyon, C., Tang, W., Wan, M., & Hu, T. Y. (2020). Clinical applications of exosome membrane proteins. *Precision Clinical Medicine*, *3*(1), 54–66. https://doi.org/10.1093/pcmedi/pbaa007

Jahangiri, B., Khalaj-Kondori, M., Asadollahi, E., Kian Saei, A., & Sadeghizadeh, M. (2023). Dual impacts of mesenchymal stem cell-derived exosomes on cancer cells: Unravelling complex interactions. *Journal of Cell Communication and Signaling*, 17(4), 1229–1247. https://doi.org/10.1007/s12079-023-00794-3

Kahlert, C., Melo, S. A., Protopopov, A., Tang, J., Seth, S., Koch, M., Zhang, J., Weitz, J., Chin, L., Futreal, A., & Kalluri, R. (2014). Identification of double-stranded genomic DNA spanning all chromosomes with mutated KRAS and p53 DNA in the serum exosomes of patients with pancreatic cancer. *Journal of Biological Chemistry*, *289*(7), 3869–3875. https://doi.org/10.1074/jbc.C113.532267

Ramos, L., T., Sánchez-Abarca, L. I., Muntion, S., Preciado, S., Puig, N., Lopez-Ruano, G., Hernandez-Hernandez, A., Redondo, A., Ortega, R., & Rodriguez, C. (2016). MSC surface markers (CD44, CD73, and CD90) can identify human MSC-derived extracellular vesicles by conventional flow cytometry. *Cell Communication and Signaling*, *14*, 1–14.

Lin, Z., Wu, Y., Xu, Y., Li, G., Li, Z., & Liu, T. (2022). Mesenchymal stem cell-derived exosomes in cancer therapy resistance: Recent advances and therapeutic potential. *Molecular Cancer*, *21*(1), 179. https://doi.org/10.1186/s12943-022-01650-5

Lu, G. D., Cheng, P., Liu, T., & Wang, Z. (2020). BMSC-derived exosomal miR-29a promotes angiogenesis and osteogenesis. *Frontiers in Cell and Developmental Biology*, *8*, 608521. https://doi.org/10.3389/fcell.2020.608521

Nakano, M., Kubota, K., Hashizume, S., Kobayashi, E., Chikenji, T. S., Saito, Y., & Fujimiya, M. (2020). An enriched environment prevents cognitive impairment in an Alzheimer's disease model by enhancing the secretion of exosomal microRNA-146a from the choroid plexus. *Brain, Behavior, and Immunity – Health*, 9, 100149. https://doi.org/10.1016/j.bbih.2020.100149

Nazarie, S.-R., Gharbia, S., Hermenean, A., Dinescu, S., & Costache, M. (2021). Regenerative potential of mesenchymal stem cells'(MSCs) secretome for liver fibrosis therapies. *International Journal of Molecular Sciences*, *22*(24), 13292.

Nikfarjam, S., Rezaie, J., Zolbanin, N. M., & Jafari, R. (2020). Mesenchymal stem cell derived-exosomes: A modern approach in translational medicine. *Journal of Translational Medicine*, *18*(1), 449. https://doi.org/10.1186/s12967-020-02622-3

Tan, S. J. O., Floriano, J. F., Nicastro, L., Emanueli, C., & Catapano, F. (2020). Novel applications of mesenchymal stem cell-derived exosomes for myocardial infarction therapeutics. *Biomolecules*, *10*(5), 707. https://doi.org/10.3390/biom10050707

Riazifar, M. (2017). *Therapeutic applications of mesenchymal stem cell vesicles*. University of California Irvine.

Simeone, P., Bologna, G., Lanuti, P., Pierdomenico, L., Guagnano, M. T., Pieragostino, D., Del Boccio, P., Vergara, D., Marchisio, M., Miscia, S., & Mariani-Costantini, R. (2020). Extracellular vesicles as signaling mediators and disease biomarkers across biological barriers. *International Journal of Molecular Sciences*, *21*(7), 2514. https://doi.org/10.3390/ijms21072514

Tomar, D., Yadav, A. S., Kumar, D., Bhadauriya, G., & Kundu, G. C. (2020). Non-coding RNAs as potential therapeutic targets in breast cancer. *Biochimica et Biophysica Acta. Gene Regulatory Mechanisms*, *1863*(4), 194378. https://doi.org/10.1016/j.bbagrm.2019.04.005

Wang, X., Tang, Y., Liu, Z., Yin, Y., Li, Q., Liu, G., & Yan, B. (2021). The application potential and advance of mesenchymal stem cell-derived exosomes in myocardial infarction. *Stem Cells International*, *2021*, 5579904. https://doi.org/10.1155/2021/5579904

Williams, A. M., Dennahy, I. S., Bhatti, U. F., Halaweish, I., Xiong, Y., Chang, P., Nikolian, V. C., Chtraklin, K., Brown, J., Zhang, Y., Zhang, Z. G., Chopp, M., Buller, B., & Alam, H. B. (2019). Mesenchymal stem cell-derived exosomes provide neuroprotection and improve long-term neurologic outcomes in a swine model of traumatic brain injury and hemorrhagic shock. *Journal of Neurotrauma*, *36*(1), 54–60. https://doi.org/10.1089/neu.2018.5711

Xu, J. H., Liang, J. P., Zhu, C. J., & Lian, Y. J. (2022). Mesenchymal stem cell-derived extracellular vesicles therapy for pulmonary hypertension: A comprehensive review of preclinical studies. *Journal of Interventional Cardiology*, *2022*, 5451947. https://doi.org/10.1155/2022/5451947

Xunian, Z., & Kalluri, R. (2020). Biology and therapeutic potential of mesenchymal stem cell-derived exosomes. *Cancer Science*, *111*(9), 3100–3110. https://doi.org/10.1111/cas.14563

Yu, Z., Teng, Y., Yang, J., & Yang, L. (2024). The role of exosomes in adult neurogenesis: Implications for neurodegenerative diseases. *Neural Regeneration Research*, *19*(2), 282–288. https://doi.org/10.4103/1673-5374.379036

Yue, R., Lu, S., Luo, Y., Zeng, J., Liang, H., Qin, D., Wang, X., Wang, T., Pu, J., & Hu, H. (2022). Mesenchymal stem cell-derived exosomal microRNA-182-5p alleviates myocardial ischemia/reperfusion injury by targeting GSDMD in mice. *Cell Death Discovery*, *8*(1), 202. https://doi.org/10.1038/s41420-022-00909-6