The Scientific Journal of Egypt Scholars Organization

Egy Sch J (2022) 1:4–7
https://doi.org/10.52649/egscj22632987

EDITORIAL

Highlight report : Therapeutic miRNAs in mesenchymal stem cells and their derived extracellular vesicles in rheumatoid arthritis

Mai Abdelgawad [1], Rabab Mostafa [2], Shorouk A. Abdelmo'tie [2], Kholoud K. Elsamman [2], Aya Hussein [2], Reham H. Mohammed [2], Hoda Y. Abdallah *[3,4]

[1] Faculty of Postgraduate Studies for Advanced Sciences (PSAS), Beni-Suef University, Beni-Suef, Egypt.
[2] Egypt scholars Lab-8 student, Egypt Scholar Organization, Egypt.
[3] Departments of Histology and Cell Biology (Genetics Unit), Faculty of Medicine, Suez Canal University, Ismailia, Egypt.
[4].Center of Excellence in Molecular & Cellular Medicine, Faculty of Medicine, Suez Canal University, Ismailia, Egypt.
*Corresponding author: hoda_ibrahim1@med.suez.edu.eg (H.Y.A).

Keywords: miRNAs; Stem cells; Rheumatoid arthritis

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease influenced by genetic, epigenetic, and environmental factors leading to a sequence of events that induce synovitis and consequent destructive arthritis. RA causes severe chronic joint inflammation in hands, knees, and feet, resulting in joint swelling, stiffness, and pain (Iain B. McInnes & Georg Schett, 2011). Cell-based therapy with mesenchymal stem cells (MSCs) and/or their derived extracellular vesicles (EVs), particularly exosomes, represent a promising treatment for RA patients. MSCs are potent, thin, fibroblast-like stem cells found in nearly all tissues and organs. MSCs are characterized by self-renewal and differentiation into several different cell types. Because of their genetic stability, immunomodulatory roles, and ability to repair damaged or inflamed tissues, MSCs have a promising role in therapeutic applications in degenerative, inflammatory, and autoimmune diseases such as RA (Guitynavard & Aghamir, 2020). EVs are double-layer lipid membranes enclosing cytosol, and they contain proteins, lipids, and nucleic acids, including microRNAs (miRNAs) (Andaloussi et al., 2013). They are released from various types of cells and function as the inter-cellular way of communication among cells (Ryan et al., 2021). According to the size and the way of secretion, the known EVs are divided into exosomes, microvesicles, and apoptotic bodies (Ryan et al., 2021).

MSCs are one of the most common known cells to produce EVs (Liu et al., 2020). MSC-derived EVs are believed to produce the same anti-inflammatory and immune-modulatory effects as their parent cells (J. J. Li et al., 2019). They are more safe and controllable than MSCs, which are highly likely to be transformed into tumor cells (Caplan et al., 2019). MiRNAs belong to small non-coding RNAs (22 nts), involved in various biological processes, and they serve as signaling molecules regulating cell-cell communications. Furthermore, they control mRNA translation through gene silencing at the posttranscriptional level (O'Brien et al., 2018). MiRNAs, expressed in or delivered to MSCs and MSC-derived EVs and exosomes, contribute to RA treatment and affect the disease pathophysiology and progress. In a collagen-induced arthritis (CIA) animal model, an animal model for RA, MSCs administration ameliorated the disease via inhibition of the NF-κB signaling pathway, which is done through downregulating miR-548e in the affected joints. MiR-548e suppressed this signaling pathway way via inhibiting the expression and translation of IκB protein, NF-κB inhibitor, through binding with the 3′-UTR of its mRNA (Yan et al., 2016). On the other hand, miRNA-23b showed its therapeutic effect against RA as an inhibitor of matrix metalloproteinases (MMP-9, MMP-2). When combined with H-89, the differentiation of synovial fluid-derived MSCs into chondrocytes occurs by targeting and suppressing the protein kinase A (PKA) signaling pathway (Ham et al., 2014). On the other hand, miRNAs can be used as a biomarker for RA patients' response to MSCs therapy. Because of individual response variation to cell-based therapy in RA, categorizing patients and stratifying them could help predict their response

and the efficacy outcome. A study done by Mallinson, Dunbar, Ridha et al. is the first of its kind to investigate and identify circulating miRNAs stratifications and link them to the treatment with expanded allogeneic adipose-derived mesenchymal stem cells (eASCs) in RA patients. In the responder eASCs treated group of RA patients, there have been three miRs (miR-26b-5p, miR-487b-3p, and miR-495-3p) that were noticeably upregulated compared with the non-responder group of patients, suggesting that these miRNAs have the potential to be stratification biomarkers for RA patients' response to eASCs (Mallinson et al., 2017). This finding could open a new avenue for tailor-making treatment for RA patients. On the other hand, miRNAs are found to be involved in the therapeutic mechanism of action of MSC-derived EVs in RA, as they are found to highly express particular types of miRNAs. For instance, bone marrow mesenchymal stem cell-derived extracellular vesicles (BM-MSC-derived EVs) alleviate RA via its miRNA-21. BM-MSC-derived EVs transfer miRNA-21, which is highly expressed, into Fibroblast-like synoviocyte (FLS), and miRNA-21 targets the TET1/KLF4 regulatory axis, leading to a decline in the KLF4 expression. This, in turn, promotes the FLS cell proliferation, suppresses the expression of the inflammatory cytokines (TNF-α, PGE2, and IL-1β), and reduces the clinical symptoms of RA (G. Q. Li et al., 2021). Other BM-MSC-derived EVs with highly expressed miRNA-34a, diminish RA inflammation by targeting cyclin I and activating the ATM/ATR/p53 signaling pathway. This, in turn, inhibits aberrant RA-FLS development and causes RA-FLS apoptosis, and therefore reduces RA inflammation. (Wu et al., 2021).

Exosomes derived from MSCs play a substantial role in RA treatment strategy because they present in different cell types, they can invade the circulating system and they contain miRNAs. Moreover, they can be used as a means for drug delivery and targeting particular cell types for treating RA patients. MSC-derived exosomes can be genetically modified, transfected to overexpress potential therapeutic miRNAs for managing RA disease. For instance, a preclinical study of the therapeutic use of MSC-derived exosomes overloaded microRNA-192a-5p demonstrated its efficacy in alleviating the inflammatory condition in CIA rats by targeting RAC2 (Zheng et al., 2020). Meng et al. (Q. Meng & Qiu, 2020) have illustrated a way by which they can regulate the behavior of FLSs in RA patients through controlling the expression of miRNAs. MSC miR-320a packed exosomes, were reported to regulate the production of CXCL9, a member of the CXC chemokine family, which was found to be significantly upregulated with concomitant downregulation of miR-320a in patients with RA and contributed to the disease.

Using MSC-derived exosomes over-expressing microRNA-320a showed a decrease in the process of activation, migration, and invasion of RA-FLSs in vitro and a decrease in the inflammatory response in CIA mice, suggesting a high therapeutic value that could come from regulating the expression of miR-320a in exosomes derived from MSCs (Q. Meng & Qiu, 2020). In another study, the effect of MSC-derived exosomes containing miR-150-5p showed its effect *in vitro* and *in vivo* in decreasing angiogenesis by targeting VEGF, and bone destruction by targeting MMP14. Moreover, the FLS invasion and migration were decreased (Chen et al., 2018). Meng et al. have used MSC-derived exosomes to deliver the therapeutic miRNA-124a, leading to proliferation inhibition in addition to migration as well as apoptosis of the FLS (H. Y. Meng et al., 2020). Similarly, MSC-derived exosomes were used as a means to transfer miRNAs among cells and permit cell-cell communication. In a study done by Tavasolian et al., miR-146a/miR-155-transduced MSC-derived exosomes were used in a CIA mice model, and the result revealed that the disease is ameliorated significantly in comparison to control mice. Such modification with anti-inflammatory miRNAs permits MSCs exosomes to treat inflammatory diseases, including RA (Tavasolian et al., 2020).

In conclusion, MSCs and MSC-derived EVs, particularly exosomes represent a promising tool for treating RA patients via particular types of miRNAs. MSC-derived exosomes can also be used as a means of delivery for therapeutic miRNAs. Little is known about the expressed miRNAs in MSCs, and MSC-derived EVs used in RA. Further investigations are required to profile these miRNAs and elucidating their targets and the involved signaling pathways.

Conflict of Interest

The authors declare no conflict of interest.

References

Andaloussi, S. E. L., Mäger, I., Breakefield, X. O., & Wood, M. J. A. (2013). Extracellular vesicles: biology and emerging therapeutic opportunities. Nature Reviews Drug Discovery, 12(5), 347–357.

Caplan, H., Olson, S. D., Kumar, A., George, M., Prabhakara, K. S., Wenzel, P., Bedi, S., Toledano-Furman, N. E., Triolo, F., & Kamhieh-Milz, J. (2019). Mesenchymal stromal cell therapeutic delivery: translational challenges to clinical application. Frontiers in Immunology, 10, 1645.

Chen, Z., Wang, H., Xia, Y., Yan, F., & Lu, Y. (2018). Therapeutic Potential of Mesenchymal Cell–Derived miRNA-150-5p–Expressing Exosomes in Rheumatoid Arthritis Mediated by the Modulation of MMP14 and VEGF. The Journal of Immunology, 201.(٨)

Guitynavard, F., & Aghamir, S. M. K. (2020). Overview of Mesenchymal Stem Cells. Mesenchymal Stem Cells, 7–13.

Ham, O., Lee, C. Y., Song, B. W., Lee, S. Y., Kim, R., Park, J. H., Lee, J., Seo, H. H., Lee, C. Y., Chung, Y. A., Maeng, L. S., Lee, M. Y., Kim, J., Hwang, J., Woo, D. K., & Chang, W. (2014). Upregulation of miR-23b enhances the autologous therapeutic potential for degenerative arthritis by targeting PRKACB in synovial fluid-derived mesenchymal stem cells from patients. Molecules and Cells, 37.(٦)

Iain B. McInnes, & Georg Schett. (2011). The Pathogenesis of Rheumatoid Arthritis. The New England Journal of Medicine, 365:2205-19.doi: 10.1056/NEJMra1004965.

Li, G. Q., Fang, Y. X., Liu, Y., Meng, F. R., Wu, X., Zhang, C. W., Zhang, Y., Liu, Y. Q., & Liu, D. (2021). MicroRNA-21 from bone marrow mesenchymal stem cell-derived extracellular vesicles targets TET1 to suppress KLF4 and alleviate rheumatoid arthritis. Therapeutic Advances in Chronic Disease, 12 .

Li, J. J., Hosseini-Beheshti, E., Grau, G. E., Zreiqat, H., & Little, C. B. (2019). Stem cell-derived extracellular vesicles for treating joint injury and osteoarthritis. Nanomaterials, 9(2), 261.

Liu, H., Li, R., Liu, T., Yang, L., Yin, G., & Xie, Q. (2020). Immunomodulatory Effects of Mesenchymal Stem Cells and Mesenchymal Stem Cell-Derived Extracellular Vesicles in Rheumatoid Arthritis. Frontiers in Immunology, 11(August), 1–7.

Mallinson, D. J., Dunbar, D. R., Ridha, S., Sutton, E. R., Rosa, O. D. la, Dalemans, W., & Lombardo, E. (2017). Identification of Potential Plasma microRNA Stratification Biomarkers for Response to Allogeneic Adipose-Derived Mesenchymal Stem Cells in Rheumatoid Arthritis. STEM CELLS Translational Medicine, 6(4), 1202–1206.

Meng, H. Y., Chen, L. Q., & Chen, L. H. (2020). The inhibition by human MSCs-derived miRNA-124a overexpression exosomes in the proliferation and migration of rheumatoid arthritis-related fibroblast-like synoviocyte cell. BMC Musculoskeletal Disorders, 21(1), 1–10.

Meng, Q., & Qiu, B. (2020). Exosomal MicroRNA-320a Derived From Mesenchymal Stem Cells Regulates Rheumatoid Arthritis Fibroblast-Like Synoviocyte Activation by Suppressing CXCL9 Expression. Frontiers in Physiology, 0, 441.

O'Brien, J., Hayder, H., Zayed, Y., & Peng, C. (2018). Overview of microRNA biogenesis, mechanisms of actions, and circulation. Frontiers in Endocrinology, 9, 1–12.

Ryan, S. T., Hosseini-Beheshti, E., Afrose, D., Ding, X., Xia, B., Grau, G. E., Little, C. B., McClements, L., & Li, J. J. (2021). Extracellular vesicles from mesenchymal stromal cells for the treatment of inflammation-related conditions. International Journal of Molecular Sciences, 22(6), 1–34.

Tavasolian, F., Hosseini, A. Z., & Naderi, S. S. and M. (2020). miRNA-146a Improves Immunomodulatory Effects of MSC-derived Exosomes in Rheumatoid Arthritis. In Current Gene Therapy (Vol. 20, Issue 4, pp. 297–312).

Wu, H., Zhou, X., Wang, X., Cheng, W., Hu, X., Wang, Y., Luo, B., Huang, W., & Gu, J. (2021). miR-34a in extracellular vesicles from bone marrow mesenchymal stem cells reduces rheumatoid arthritis inflammation via the cyclin I/ATM/ATR/p53 axis. Journal of Cellular and Molecular Medicine, 25(4), 1896–1910.

Yan, X., Cen, Y., & Wang, Q. (2016). Mesenchymal stem cells alleviate experimental rheumatoid arthritis through microRNA-regulated I? B expression. Scientific Reports, 6(February), 1–12.

Zheng, J., Zhu, L., Iok In, I., Chen, Y., Jia, N., & Zhu, W. (2020). Bone marrow-derived mesenchymal stem cells-secreted exosomal microRNA-192-5p delays inflammatory response in rheumatoid arthritis. International Immunopharmacology, 78, 105985.

Acknowledgement

The authors thank Egypt Scholars, especially Egypt Scholar Labs for their effort.

About Egypt Scholars

Egypt Scholars is an independent, non-profit organization founded on the principle of volunteerism. The organization includes volunteers with expertise in various fields ranging from scientific research and entrepreneurship to law, humanities and the social sciences. Arising from its strong belief in the infinite benefits of volunteerism, the members collaborate on a voluntary basis to facilitate the exchange of scientific and professional knowledge, skills and expertise both within Egypt and internationally. Egypt Scholars is a 501c-3 tax-exempt non-profit organization registered in California.