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OPTIMIZING QUALITY AND SAFETY OF MESENCHYMAL STEM CELLS DERIVED EXOSOMES FOR CLINICAL USE : A REVIEW

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ABSTRACT Exosomes are nanovesicles with a wide range of chemical compositions used in many different applications. Mesenchymal stem cell-derived exosomes (MSCs-EXOs) are spherical vesicles that have been shown to mediate tissue regeneration in a variety of diseases, including neurological, autoimmune and inflammatory, cancer, ischemic heart disease, lung injury, and liver fibrosis. They can modulate the immune response by interacting with immune effector cells due to the presence of anti-inflammatory compounds and are involved in intercellular communication through various types of cargo. MSCs-EXOs exhibit cytokine storm-mitigating properties in response to COVID-19. This review discussed the potential function of MSCs-EXOs in a variety of diseases including neurological, notably epileptic encephalopathy and Parkinson's disease, cancer, angiogenesis, autoimmune and inflammatory diseases. We provided an overview of exosome biogenesis and factors that regulate exosome biogenesis. Additionally, we highlight the functions and potential use of MSCs-EXOs in the treatment of the inflammatory disease COVID-19. Finally, we covered a strategies and challenges of MSCs-EXOs. Finally, we discuss conclusion and future perspectives of MSCs-EXOs.

KEYWORDS : Extracellular Vesicle, Biogenesis, Mesenchymal Stem Cells, Exosomes, Autoimmune Disease, Angiogenesis

INTRODUCTION

Generally, extracellular vesicles (EVs) are a heterogeneous group of cell-derived membranous nanovesicles generated from cells that range in size from 30 to 1000 nm. Based on size and origin, EVs are classified into exosomes, microvesicles (MVs), and apoptotic bodies (ABs).[1] They are released from most cell types and bio-fluids such as blood, saliva, breast milk, semen, urine, cerebrospinal fluid (CSF), colostrum,tears, bronchoalveolar fluid, epididymal fluid, amniotic fluid, bile, blastocoel fluid, middle ear effusion, and ascites. Exosomes are having with an average size between 30 and 150 nm, which are a subset of extracellular vesicles and are important messengers of paracrine activity. Tetraspanins (CD9, CD63, and CD81), heat shock proteins (HSPs), membrane transporters and fusion proteins, multivesicular bodies (MVBs) proteins, phospholipases, and lipid-related proteins are considered to be biomarkers found in exosomes.[2,3] The biogenesis and secretion of exosomes occurs by the formation of MVBs and fuse with the plasma membrane and eventually leads to secretion of cargoes in the extracellular milieu.[4] Exosomes are subset of EVs, which are playing vital role in physiological and pathological conditions, such as cellular junctions, integrins, and selectins.[5]

Exosomes are found abundantly in the secretome of many cell types such as embryonic stem cells, and induced pluripotent stem cells (iPSCs).[6] Exosomes are vesicles that carry a variety of bioactive substances, including proteins, DNA, soluble and membrane proteins, microRNAs (miRNAs), and nucleic acids. These exosomes are a reflection of the cell from which they were produced as well as of the biogenesis and release routes. Exosomes are produced by nearly all forms of life and are present in a variety of bodily fluids. They have a variety of roles in cellular processes such as intercellular communication, immunological regulation, senescence, proliferation, and differentiation.[7] Exosomes produced from iPSCs are believed to be therapeutic agents as targeted delivery agents and are safer than parental cells. They can promote a variety of functions, including angiogenesis, extracellular matrix (ECM) remodelling, and immune response regulation.[8] Exosomes can transport exogenous bioactive substances and can pass the blood-brain barrier. Exosomes, for instance, are employed as indicators or therapy options for a number of diseases, such as cancer, neurological disorders, and immune-related illnesses.[9]

MSC-derived exosomes (MSC-EXOs) are nanosized vesicles that have demonstrated therapeutic efficacy in the treatment of a number of diseases, including liver diseases, kidney diseases, brain diseases and cardio vascular diseases (CVDs) through interaction with their target cells through a variety of mechanisms, such as interaction, fusion, and internalisation of exosomes with the plasma membrane of recipient cells and these vesicles are necessary for cell-cell communication. The exosome cargoes that are released into physiological fluids mediate cell-cell contacts and regulate a variety of cellular processes. These mediators are crucial for the regulation of a variety of vital functions of their target cells to maintain homeostasis.[10,]

Recent research suggests that active exosomes produced by stem cells can prevent heart and blood vessel illnesses by carrying a variety of payloads, including as proteins, miRNAs, and lncRNAs, to nearby or distant target cells. According to studies, the payloads and functions of exosomes produced by various types of cells varies greatly.For instance, EVs produced from cancer stem cells (CSCs) carry out a variety of biological activities, such as metastasis, angiogenesis, immunosuppression, and resistance to treatment.[11,] In order to maintain tumour heterogeneity, CSCs release EVs that communicate certain proteins and transcription factors to nearby cells.[12] Recent research suggests that MSC-EXOs could be used to treat inflammatory and autoimmune illnesses since MSCs have immunosuppressive qualities. Through the transport of parental cell cargo, MSCs' paracrine characteristics play a crucial role in cell-to-cell communication and are also implicated in the innate and adaptive immune response. MSC-EXOs are capable of triggering the necessary response in the event of injury, inflammation, or repair due to their dynamic immunomodulatory function. According to numerous research, MSC-EXO's bioactive chemicals and anti-inflammatory molecules interact with immune effector cells to play a vital role in immune response and control. These properties can be used to treat autoimmune illnesses. Exosomes produced by neurons, astrocytes, oligodendrocytes, and microglia and found in serum are thought to be early indicators of CNS illnesses, particularly neurodevelopmental disorders.[13] Exosomes may be able to stop the loss of neurons by specifically attaching to target cells in the central nervous system. Pilocarpine-induced epilepsy was shown to reduce

inflammation and memory impairment by MSC-EXOs by targeting hippocampus astrocytes in a mouse in vivo investigation. Particularly, Parkinson's disease (PD), which affects about 1% of persons over, is the second most common neurodegenerative disease in the world. Among these paracrine effectors, MSC-EVs are a significant contributor and have the property of becoming a directed anti-tumor drug delivery platform or agent.[14]The MSC-EXOs cargo has positive cardioprotective effects as a result of transporting and distributing a range of substances to the wounded cells. MSC-EXOs have demonstrated efficacy as minimally invasive agents for the repair, regeneration, and protection of human organs against a variety of bodily injuries. Stem cell secretome (SCS) released exosomes shows significant anti-fibrotic, anti-inflammatory, immunomodulatory, and anti-angiogenic actions.[15]

Considering all the literatures into account, in this review, we discuss general aspects of biogenesis and factors involved in promotion of biogenesis and secretion of exosomes and we also discuss in detail account about the role of MSC-EXOs in various diseases including neurological diseases, epileptic encephalopathy and Parkinson's. Further, we discuss the involvement of MSC-EXOs in cardiovascular, cancer, angiogenesis and autoimmune and inflammatory diseases and specifically multiple sclerosis, rheumatoid arthritis, type 1 diabetes mellitus, uveitis, systemic lupus erythematosus, inflammatory bowel disease and COVID-19. Besides, this review summarizes the current advances of potential therapeutic benefits, underlying mechanisms, diagnosis, treatment, challenge and strategies of use of MSC-EXOs and limitations of mesenchymal stem cell-derived exosomes in various types of diseases.[16]

Role of MSC-EXOs in Neurological Disease

Human pluripotent stem cell-derived EVs are essential for several biological functions, including the protection of tissue homeostasis. The recipient cells experience protective benefits, reduced oxidative stress, and apoptosis after receiving EVs produced from stem cells. In addition to forming myelin, releasing neurotransmitters, and providing glia-mediated trophic support to axons, the EVs released by neuronal cells like oligodendrocytes are also capable of communicating with other cells via miR-219.[17,]

Role of MSC-EXOs in Epileptic Encephalopathy

Multiple factors contribute to epilepsy, which is a highly synchronised aberrant discharge of brain neurons that affects both health and behaviour. Epilepsy affects over 65 million people worldwide.[170] Exosomes were often isolated from a variety of physiological fluids, including cerebrospinal fluid, blood, urine, and other biological fluids.[18] MSC-EXOs have demonstrated positive effects on several neurological conditions, including stroke, multiple sclerosis, Alzheimer's disease (AD), SCI, ischemia, traumatic brain injury, hypoxic-ischemia produced prenatal brain injury and preterm brain injury. The microRNAs found in exosomes from patients with epilepsy and depression's CSF fluid may be able to traverse the blood-brain barrier.[19,] By specifically connecting with target nervous system cells, exosomes control neuroinflammation of the central nervous system.

Role of MSC-EXOs in Parkinson's Disease

The second most prevalent neurological disease in the world is Parkinson's disease (PD). Nearly 0.3% of the population has PD, and those over the age of 65 make up 1% of those who are affected.Clinical signs of Parkinson's disease (PD) patients include bradykinesia, postural instability, and resting tremor. Dopaminergic neurons in the SNpc are still dying, which is one of many mechanisms that contribute to the pathophysiology of PD.The histological development of Lewy bodies, which predominately contain misfolded α-synuclein, is a hallmark of Parkinson's disease.[20]

Role of MSC-EXOs in Cardiovascular Diseases

Cardiovascular diseases (CVDs) are a major cause of mortality worldwide and have become a public health priority. The main causes of CVDs are low levels of cardiac progenitor cell proliferation and insufficient myocyte proliferation in existing myocytes. Recent research has shown that MSC-EXOs are important in cardio-protective functions. Stem/progenitor cell transplantation is regarded as an effective therapeutic approach that can replace missing cardiomyocytes and enhance contractility.[21]

Role MSC-EXOs in Cancer

Exosomes produced by MSCs are crucial for both drug resistance and pro-angiogenesis. MSCs have the power to trigger immunological responses, tissue healing, cell proliferation, and tumour progression control.[22] As regulators of the tumour niche, MSCs release exosomes, and their involvement in tumorigenesis and metastasis is controlled by a number of growth factor receptors, including EGFR and PDGFR. Through the AKT (protein kinase B), PKC, and MAP kinase pathways, the activation of these receptors by intracellular kinases causes downstream pro-growth signals to be released, which promotes the growth of tumour cells by activating the AKT/ERK1/2 signalling pathway.[23] Through the activation of pathways like p53, AKT, and c-Jun N-terminal kinase (JNK), BM-MSC-EXOs promoted proliferation and migration. BM-MSC-EXOs contains miR-221 potentially accelerating their growth and increasing their invasive capacity. MSC-EXOs promote the growth and spread of breast cancer by activating Wnt signalling and establishing a favourable microenvironment.

Role of MSC-EXOs in Autoimmune and Inflammatory Diseases

Studies have been focused on EVs, which are utilized as a cell-free therapy and elucidate its potential significance of MSC-EXOs in the treatment of autoimmune diseases. Autoimmune diseases are potentially influencing multiple organs and systems, such as circulatory, respiratory, the motor and digestive system. Compared to men, women are more affected. Glucocorticoids and immunosuppressive medications are the only therapy for autoimmune illness that are currently accessible. However, using steroids frequently results in undesirable side effects.[24]

Multiple Sclerosis (MS)

The central nervous system (CNS) is affected by the chronic autoimmune and inflammatory disease known as multiple sclerosis. The most widely utilised animal model of MS is called experimental autoimmune encephalomyelitis (EAE). The CNS is the primary pathogenic component in MS, and it is activated and recruited by auto-aggressive CD4+ and CD8+ T cells. Therapies that treat diseases might have undesirable side effects. MSC-EXOs were used to create an alternate manner of treatment. By delivering the tolerogenic molecules to the autoreactive immune cells,

Rheumatoid Arthritis (RA)

RA is a long-lasting, inflammatory, and systemic autoimmune condition characterised by symptoms of joint degeneration and eventual loss of function brought on by both genetic and environmental causes.[25,] Disorders of innate and adaptive immunity, which lead to immune complex-mediated complement activation, are defining characteristics of RA.[26] Antibodies or soluble decoy receptors are used to combat pro-inflammatory cytokines such GM-CSF, TNF-, and IL-6. Recent research suggests that MSC-EXOs decrease the immune system's response to RA.Injection of co-gene DBA/1 fibroblasts secreting GAL-1 slowed the progression of arthritis by preventing proliferation and lowering the proportion of mature T and B cell subsets. MSC-EXOs have been shown to have anti-inflammatory effects on T and B lymphocytes in the collagen-induced arthritis (CIA) mouse model.[27]

Type 1 Diabetes Mellitus (Insulin-Dependent Diabetes Mellitus)

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease influenced by genetic, immune, and environmental factors. Insulin resistance and low insulin levels are caused by the autoimmune loss of pancreatic cells that produce insulin. The cause of type 1 diabetes and its contributing variables are the loss of immunological tolerance in autoreactive B cells, CD4+T cells, and CD8+.[28]

Uveitis

Uveitis is an autoimmune condition that severely impairs vision. Corticosteroids were employed to overcome the vision impairment. However, prolonged steroid use results in glaucoma. Consequently, a fresh approach to treatment is required. For instance, Bai et al showed that MSC-EXOs from the human umbilical cord lessened the severity of EAU by preventing inflammatory leukocyte infiltration into the eyes.[29]

Inflammatory Bowel Disease (IBD)

IBD is a chronic, nonspecific, relapsing inflammatory gastrointestinal disease. MSC- EXOs components have potential targets for the diagnosis and treatment of IBD. For instance, an in vivo study using mouse model of IBD revealed that hUC-MSC-EXOs treatment decreased the infiltration of macrophages in colon tissue and inhibited the expression of IL-7.[30] MSC-EXOs carrying miR-146a, effectively down-regulated TNF receptor-associated factor 6 (TRAF6) and IL-1 receptor associated kinase 1 (IRAK1) expression, inhibited pro-inflammatory cytokine and enhanced the expression of IL-10. hUC-MSC-EXOs protects intestinal barrier by down regulation of pro-inflammatory cytokines in colon tissue, and up-regulated the levels of anti-inflammatory cytokines.[31]

Role of MSC-EXOs on COVID-19

Patients who had immune-mediated inflammatory diseases were impacted by COVID-19 and were thought to be at a high risk of contracting SARS-CoV-2 and developing severe COVID-19. An overwhelming host immunological response, or "cytokine storm", caused by COVID-19 is characterised by an overproduction of growth factors, chemokines, and pro-inflammatory cytokines like TNF and IL-6.[32] Targeting pro-inflammatory cytokines are the best tools and are therapeutic targets in the treatment of patients affected by immune-mediated inflammatory diseases and also involved in re-generation.[33] Hence, to find out effective therapies for the treatment of patients with severe stages of the disease like COVID-19 is inevitable MSC-EXOs can promote the survival of alveolar macrophages and change their phenotype from pro-inflammatory (M1) into the anti-inflammatory (M2) polarization, which has been confirmed by at least two studies.[34]

The Potential of MSC-EXOs in the Treatment of COVID-19

The primary pathogenesis of COVID-19 is overactivation of the immune system. MSCs are known to induce anti-inflammatory macrophages, regulatory T cells and dendritic cells. At present, the treatment for COVID-19 is mostly symptomatic and supportive, though anti-inflammatory and antiviral treatment has been employed.[35] MSC-exosomes are able to transfer cargoes to target cells and tissues, resulting in changes to gene expression and in the behavior of target cells. MSC-derived exosomes as cell-free therapeutics due to the unique properties of MSC-EXOs including high stability, low immunogenicity, easy storage, and ability to cross the blood-brain barrier compared to their counter parts.6 [36] MSC-secreted exosomes are shown to both regulate immunity through interacting with immune cells and inhibit the inflammatory response through cytokines.[37]

Challenges and Strategies of Use of MSC-EXOs

The important challenges for the application exosomes derived from stem cells is to identify the molecules involved in paracrine action of stem cells, which facilitate to open new therapeutics avenues using exosomes including the production, processing and manufacturing aspects, particularly isolation, purification and characterization.[38] Although, variety of isolation techniques/methods are available such as ultracentrifugation, size, immunoaffinity captured, precipitation and microfluidics, still to prepare clinical grade exosomes are critical factor. Another important factor is, there is no uniform method to separate exosomes, and also each and every method has its own advantages and disadvantages. Therefore, MSC-EXOs separation methods must be uniform and standardized. For instance, the contents of cargoes are different among various separating methods. For example, ultracentrifugation is well known and common method, which produces significant purity but the yield is low. Therefore, it is required to explore a more efficient method for purification and yield and near future developments. The most important obstacle is the yield of exosomes, which can be improved using combination of currently available methods such as 3D microcarrier-based suspension culture promoted by certain bio-active materials. To increase the yield, engineering of full artificial exosomes is necessary which can be relatively controllable composition and clear therapeutic pathway.

The next challenge is source of EVs/exosomes. Physiological conditions and behavior of cells are important factor to provide consistent exosome quality and yield. Next, the important challenge is isolation and storage of exosomes, which are critical, adequate and appropriate technologies to produce quality exosomes for the safety of both donor and recipients. Although exosomes have great potential to treat various types of diseases, still several challenges are remained elusive. The important task is, the source and contents of the exosomes derived from various culture conditions must be determined using standardized protocol and also the conditions of storage, preservation, half-life of freshly isolated and cryopreserved exosomes and also transportation of exosomes needs to be solved. Further challenges are warranted to understand and precise determination of exact components involved to treat neurological, particularly epileptic encephalopathy, Parkinson's, cancer, angiogenesis and autoimmune and inflammatory diseases. Further, several challenges are required to probe the therapeutic effect of MSC-EXOs to maintain the long-term effect, and know the facts of negative effect, which are very important criteria for the correct use of exosomes to treat various diseases. Furthermore, although MSC-EXOs are superior to MSCs, to increase the efficacy, and purification and the scale-up technology needs to be improved before it can be used in clinical practice.

Conclusion and Future Perspectives

The exosomes released from stem cells were applied for numerous healing purposes and to develop novel regenerative techniques The EVs from stem cells exert protective effects in the treatment of various diseases by regulating various pathological conditions. MSC-EXOs offer a more possibility of cell-free therapy than parental MSCs due to the regenerative and anti-inflammatory effect. The unique properties MSC-EXOs such as immunomodulatory effects allow treating different inflammatory and autoimmune diseases. Finding from several studies indicated that exosomes secreted by MSCs play significant role in cancer progression. Conversely, MSC-EXOs can also suppress tumors through regulating immune responses and intercellular signaling. MSC-EXOs used as drug delivery systems are considered to deliver targeted tumor therapy. MSC-EXOs shows potential effects on suppression of several autoreactive cells in autoimmune diseases. Due to their ability to modulate DAn survival, MSC-secretome considered as a promising therapeutic tool for several neuro-degenerative diseases.

The future perspectives need to be concentrated on various aspects including stability, long-term preservation, purification processes and the precise molecular contents are essential; it would help produce ready-to-use batches of exosomes, which could be easily transported. Culture conditions such as cell density, passage number, hypoxia, extracellular matrix, and mechanical stress can influence the production. Hence, the derived exosomes must be characterized by various analytical techniques including size distribution, TEM, SEM, Nanotrack, proteomics, and miRNA profiling, which are essential parameters for therapeutic purposes for various diseases. However, the exact mechanisms of the effects of MSC-EXOs on cancer need to be explored and tested and the utility of exosomes as a delivery vehicle. Hence, additional studies of MSC-EXOs are required to determine their roles in the pathogenesis of cancer and to provide a new tool for cancer diagnosis and therapeutics. More studies are required to illuminate unclear aspects of cell-free therapy using MSC-EXOs. Thus, understanding the complexity of MSC-EXOs, and how its miRNA content interacts with cells involved in the molecular, cellular and functional mechanisms is of great importance in all kinds of diseases. More studies are necessary to explore the molecular mechanisms of those exosomes harboring lncRNAs in the pathogenesis, potential pathways, and development of multi-target-based strategies for RA. Since exosomes are derived from various types of stem cells and may provide different response in target cells, thus detailed investigations are necessary to identify the optimal cell types, functional status, and molecular contents and engineering of exosomes are essential to provide platforms for durable retention and prolonged release of cargos in the injured myocardium. Standards and guidelines should be established for isolation, purification, and identification of surface biomarkers from the samples of diseases patients for the use of the clinical setting. Another important issue needs to resolve is to reduce the lot-to-lot variation regarding primary naive MSCs. Collectively, findings from various studies imply that MSC-derived exosomes possess promising therapeutic capacity and these can be exploited as exosome-based therapy for the treatment of a variety of diseases as drug delivery vehicle and biomarkers. However, many efforts are required towards determining standards methods to enhance effective, efficacy and safety therapy, which will speed up clinical trials and patients speed recovery by implementation of MSC-EXOs as therapeutic agents. Finally, determination of optimal dose and safety measurements are inevitable parameters for the development of an effective exosome-based nanoplatform to expand the therapeutic potential.

REFERENCES

1. Raposo G, Nijman HW, Stoorvogel W, et al. B lymphocytes secrete antigen-presenting vesicles. J Exp Med. 1996;183(3):1161–1172. doi:10.1084/jem.183.3.1161
2. Conde-Vancells J, Rodriguez-Suarez E, Embade N, et al. Characterization and comprehensive proteome profiling of exosomes secreted by hepatocytes. J Proteome Res. 2008;7(12):5157–5166. doi:10.1021/pr8004887
3. Subra C, Grand D, Laulagnier K, et al. Exosomes account for vesicle-mediated transcellular transport of activatable phospholipases and prostaglandins. J Lipid Res. 2010;51(8):2105–2120. doi:10.1194/jlr.M003657
4. Johnstone RM, Adam M, Hammond JR, Orr L, Turbide C. Vesicle formation during reticulocyte maturation. Association of plasma membrane activities with released vesicles (exosomes). J Biol Chem. 1987;262(19):9412–9420. doi:10.1016/S0021-9258(18)48095-7
5. Martins VR, Dias MS, Hainaut P. Tumor-cell-derived microvesicles as carriers of molecular information in cancer. Curr Opin Oncol. 2013;25(1):66–75. doi:10.1097/CCO.0b013e32835b7c81
6. Katsman D, Stackpole EJ, Domin DR, Farber DB. Embryonic stem cell-derived microvesicles induce gene expression changes in Müller cells of the retina. PLoS One. 2012;7(11):e50417. doi:10.1371/journal.pone.0050417
7. Zhu L, Kalimuthu S, Gangadaran P, et al. Exosomes derived from natural killer cells exert therapeutic effect in melanoma. Theranostics. 2017;7(10):2732–27451. doi:10.7150/thno.18752
8. Lamichhane TN, Sokic S, Schardt JS, Raiker RS, Lin JW, Jay SM. Emerging roles for extracellular vesicles in tissue engineering and regenerative medicine. Tissue Eng Part B Rev. 2015;21(1):45–54. doi:10.1089/ten.TEB.2014.0300
9. Liu C, Xu X, Li B, et al. Single-exosome-counting immunoassays for cancer diagnostics. Nano Lett. 2018;18(7):4226–4232. doi:10.1021/acs.nanolett.8b01184
10. Camussi G, Deregibus MC, Bruno S, Grange C, Fonsato V, Tetta C. Exosome/microvesicle-mediated epigenetic reprogramming of cells. Am J Cancer Res. 2011;1(1):98–110.
11. Sun Z, Wang L, Dong L, Wang X. Emerging role of exosome signalling in maintaining cancer stem cell dynamic equilibrium. J Cell Mol Med. 2018;22(8):3719–3728. doi:10.1111/jcmm.13676
12. Al-Sowayan BS, Al-Shareeda AT, Alrfaei BM. Cancer stem cell-exosomes, unexposed player in tumorigenicity. Front Pharmacol. 2020;11:384. doi:10.3389/fphar.2020.00384
13. Chiasserini D, van Weering JR, Piersma SR, et al. Proteomic analysis of cerebrospinal fluid extracellular vesicles: a comprehensive dataset. J Proteomics. 2014;106:191–204. doi:10.1016/j.jprot.2014.04.028
14. Baek G, Choi H, Kim Y, Lee HC, Choi C. Mesenchymal stem cell-derived extracellular vesicles as therapeutics and as a drug delivery platform. Stem Cells Transl Med. 2019;8(9):880–886. doi:10.1002/sctm.18-0226
15. Moghadasi S, Elveny M, Rahman HS, et al. A paradigm shift in cell-free approach: the emerging role of MSCs-derived exosomes in regenerative medicine. J Transl Med. 2021;19(1):302. doi:10.1186/s12967-021-02980-6
16. Barile L, Moccetti T, Marbán E, Vassalli G. Roles of exosomes in cardioprotection. Eur Heart J. 2017;38(18):1372–1379. doi:10.1093/eurheartj/ehw304
17. Zhu Y, Wang Y, Zhao B, et al. Comparison of exosomes secreted by induced pluripotent stem cell-derived mesenchymal stem cells and synovial membrane-derived mesenchymal stem cells for the treatment of osteoarthritis. Stem Cell Res Ther. 2017;8(1):64. doi:10.1186/s13287-017-0510-9
18. Guerrini R, Marini C, Barba C. Generalized epilepsies. Handb Clin Neurol. 2019;161:3–15. doi:10.1016/B978-0-444-64142-7.00038-2
19. Nolte-'t Hoen E, Cremer T, Gallo RC, Margolis LB. Extracellular vesicles and viruses: are they close relatives? Proc Natl Acad Sci USA. 2016;113(33):9155–9161. doi:10.1073/pnas.1605146113
20. Pitkänen A, Löscher W, Vezzani A, et al. Advances in the development of biomarkers for epilepsy. Lancet Neurol. 2016;15(8):843–856. doi:10.1016/S1474-4422(16)00112-5
21. Khoo TK, Yarnall AJ, Duncan GW, et al. The spectrum of nonmotor symptoms in early Parkinson disease. Neurology. 2013;80(3):276–281. doi:10.1212/WNL.0b013e31827deb74
22. Srivastava D, Ivey KN. Potential of stem-cell-based therapies for heart disease. Nature. 2006;441(7097):1097–1099. doi:10.1038/nature04961
23. Galipeau J, Sensébé L. Mesenchymal stromal cells: clinical challenges and therapeutic opportunities. Cell Stem Cell. 2018;22(6):824–833. doi:10.1016/j.stem.2018.05.004
24. Gu H, Ji R, Zhang X, et al. Exosomes derived from human mesenchymal stem cells promote gastric cancer cell growth and migration via the activation of the Akt pathway. Mol Med Rep. 2016;14(4):3452–3458. doi:10.3892/mmr.2016.5625
25. Wang JH, Liu XL, Sun JM, Yang JH, Xu DH, Yan SS. Role of mesenchymal stem cell derived extracellular vesicles in autoimmunity: a systematic review. World J Stem Cells. 2020;12(8):879–896. doi:10.4252/wjsc.v12.i8.879
26. MacGregor AJ, Snieder H, Rigby AS, et al. Characterizing the quantitative genetic contribution to rheumatoid arthritis using data from twins. Arthritis Rheum. 2000;43(1):30–37. doi:10.1002/1529-0131(200001)43:1<30::AID-ANR5>3.0.CO;2-B
27. Malmström V, Catrina AI, Klareskog L. The immunopathogenesis of seropositive rheumatoid arthritis: from triggering to targeting. Nat Rev Immunol. 2017;17(1):60–75. doi:10.1038/nri.2016.124
28. Cosenza S, Ruiz M, Toupet K, Jorgensen C, Noël D. Mesenchymal stem cells derived exosomes and microparticles protect cartilage and bone from degradation in osteoarthritis. Sci Rep. 2017;7(1):16214. doi:10.1038/s41598-017-15376-8
29. Bluestone JA, Herold K, Eisenbarth G. Genetics, pathogenesis and clinical interventions in type 1 diabetes. Nature. 2010;464(7293):1293–1300. doi:10.1038/nature08933
30. Bai L, Shao H, Wang H, et al. Effects of mesenchymal stem cell-derived exosomes on experimental autoimmune uveitis. Sci Rep. 2017;7(1):4323. doi:10.1038/s41598-017-04559-y
31. Mao F, Wu Y, Tang X, et al. Exosomes derived from human umbilical cord mesenchymal stem cells relieve inflammatory bowel disease in mice. Biomed Res Int. 2017;2017:5356760. doi:10.1155/2017/5356760
32. Yang S, Liang X, Song J, et al. A novel therapeutic approach for inflammatory bowel disease by exosomes derived from human umbilical cord mesenchymal stem cells to repair intestinal barrier via TSG-6. Stem Cell Res Ther. 2021;12(1):315. doi:10.1186/s13287-021-02404-8
33. Huang Y, Yang C, Xu XF, Xu W, Liu SW. Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. Acta Pharmacol Sin. 2020;41(9):1141–1149. doi:10.1038/s41401-020-0485-4
34. He X, Dong Z, Cao Y, et al. MSC-derived exosome promotes M2 polarization and enhances cutaneous wound healing. Stem Cells Int. 2019;2019:7132708. doi:10.1155/2019/7132708
35. Wu YC, Chen CS, Chan YJ. The outbreak of COVID-19: an overview. J Chin Med Assoc. 2020;83(3):217. doi:10.1097/JCMA.0000000000000270
36. Yin K, Wang S, Zhao RC. Exosomes from mesenchymal stem/stromal cells: a new therapeutic paradigm. Biomarker Res. 2019;7(1):8. doi:10.1186/s40364-019-0159-x
37. Yang C, Lim W, Park J, Park S, You S, Song G. Anti-inflammatory effects of mesenchymal stem cell-derived exosomal microRNA-146a-5p and microRNA-548e-5p on human trophoblast cells. Mol Hum Reprod. 2019;25(11):755–771. doi:10.1093/molehr/gaz054
38. Luan X, Sansanaphongpricha K, Myers I, Chen H, Yuan H, Sun D. Engineering exosomes as refined biological nanoplatforms for drug delivery. Acta Pharmacol Sin. 2017;38(6):754–763. doi:10.1038/aps.2017.12