BÖLÜM 38

KÖK HÜCRE KAYNAKLI EKSOZOMLAR VE ÇOCUK NÖROLOJİ PRATİĞİNDE KULLANIMI

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GİRİŞ

Eksozomlar, ekstraselüler veziküller hücreler arası iletişimde önemli bir tür aracı olarak tanımlanmıştır. Önceleri ekstraselüler veziküller sadece hücrelerin plazma membranının dışa doğru atılması veya tomurcuklanması ile salgılanan, zarla çevrili veziküller olarak düşünülürken, son yıllarda farklı oluşum mekanizmalarına sahip çeşitli hücredışı vezikül tiplerinin dokularda var olduğu belirlenmiştir.[1]

Eksozomlar, çeşitli hücre tipleri tarafından salgılanan 30 ile100 nm boyutunda veziküllerdir.[2] Eksozomların plazma membranları, hekzosilseramidler, kolesterol, fosfatidilserin, sfingomiyelin ve doymuş yağ asitleri olmak üzere çeşitli lipitlerden oluşur.[3] Kök hücre kaynaklı eksozomlarda ise ek olarak araşidonik asit (AA), lökotrienler, prostaglandinler, fosfatidik asit, dokosaheksanoik asit (DHA) ve lizofosfatidilkolin (LPC) gibi yağ asitleride bulunur.[4,5] Eksozomlarda bulunan proteinlerin çoğunluğu tetraspanin ailesine ait membran proteinleri (CD81, CD82, CD63 ve CD9), hücre membranının füzyonu sonucu oluşan multiveziküler cisimciklerin biyogenezine katkı sağlayan "Endosomal Sorting Complex Required for Transport" (ESCRT) ile ilişkili proteinler (Alix, TSG101), ısı şok proteinleri (HCP/HSP 70 ve 90) ve membran taşıma ve füzyonu için gereken proteinlerdir (Rab GTPazlar, annexinler ve flotilinler).[6,7] Aynı zamanda hücre iskeletinde bulunan proteinler (aktin, sintenin ve moezin), sinyal iletim proteinleri (kinaz proteinleri) ve metabolik enzimleri de (GAPDH, LDHA, PGK1, aldolaz ve PKM) taşır.[8]

Kök hücre kaynaklı eksozomlarda, diğer eksozomların ortak özelliklerine ek olarak CD73, CD44, CD90, CD29 gibi özel membran bağlayıcı proteinleride bulunur.[9,10] Eksozomlar sadece lipit ve protein değil, aynı zamanda konakçı hücrenin messenger RNA (mRNA) ve mikro RNA(miRNA)'sını içerir.[11,12].

Ayrıca protein ve RNA türlerine ek olarak farklı DNA çeşitleride olduğu bulunmuştur.[13,14] Yukarıda da belirtildiği gibi eksozomlarının sadece farklı hücresel fonksiyonları yoktur aynı zamanda farklı protein ve RNA içeriklerine de sahiptirler. Kök hücrenin büyümesini, çoğalmasını, yapışmasını, göçünü ve morfogenez kapasitelerini kontrol etmekle görevli kök hücre kaynaklı eksozomların 730 fonksiyonel protein içeriği tanımlamıştır.[15] Kök hücre kaynaklı eksozomlarda bulunan RNA

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hücrelerinin eksozomal miR-29 aracılığıyla DMD hastalarında kas hücrelerinin farklılaşmasını arttırdığını ve ayrıca farelerde terapötik bir etki göstererek kreatinin kinaz (CK) seviyelerini azalttığı, kalp doku ve diafram kasındaki fibrozisi ve inflamasyonu azalttığı belirtilmiş.[192] Ayrıca, distrofin eksikliği olan iskelet kasındaki fibroblastlardan sekrete edilen eksozomların fibrotik yanıtı arttırdığı gösterilmiştir.[193] Yapılan bir başka çalışmada ise, endojen kardiyomiyosit tarafından sekrete edilen eksozomların ERK1/2 ve p38 MAPK yolağını kullanarak distrofin eksikliği olan kardiyomiyositleri hücresel strese karşı koruyabileceği belirtilmiş.[194] Yine başka bir çalışmada, kardiyak kaynaklı kök hücreler ve bu hücrelerden salgılanan eksozomların sadece kardiyak değil, iskelet kasınında yapısını güçlü bir şekilde iyileştirdiği ve DMD modeli oluşturulan farelerde tam uzunlukta distrofinin kısmi ekspresyonunun geçici olarak iyileştirdiği gösterilmiştir.[195] Leng ve ark.'nın bir çalışmasında eksozomların farelere tekrarlanan sistemik uygulamasının, bozulan kas fonksiyonu ve kas yapısını geri düzenlediği, toksisite olmadan patolojik ilerlemeyi durdurduğu gösterilmiş, eksozomlar ekzon atlama veya genom düzenleme terapileri ile kombinasyon halinde kullanıldığında sinerjik bir etki ortaya çıkarabileceği ve DMD için tedavi seçeneklerinden biri olabileceği belirtilmiştir.[196]

Myastenia Gravis: Myastenia Gravis (MG), asetilkolin reseptör antikorlarına (AChR), düşük yoğunluklu lipoprotein reseptörü ile ilişkili protein 4'e (LRP4) veya kaslara özgü kinaz (MuSK) karşı otoantikor üretimi sonucunda gelişen, kaslarda jeneralize veya lokalize tutulum oküler ve/veya bulber yorgunluk ile karakterize olabilen otoimmün sistemik bir hastalıktır, bu hastalarda ciddi bir miyastenik kriz sırasında pitozis bu hastalarda ciddi bir miyastenik kriz sırasında pitozis, diplopi, dizartri, disfaji ve proksimal ekstremite güçsüzlüğü gibi ağır klinik tablo ortaya çıkabilir.[197-199] Eksozomların düşük antijenite ve immünojeniteye özelliğine sahip olması ve eksozomların sinyal yollarını düzenleyebilmesi nedeniyle, eksozomları otoimmün bozukluklar da dahil olmak üzere çeşitli hastalıklarda umut vaad edici bir tedavi seçeneği haline getirmiştir.[200] Yapılan bir çalışmada, otoimmün myastenia gravis modeli oluşturulan farelerde immatür dentritik hücre kaynaklı eksozomların AChR-reaktif lenfosit proliferasyonunu, AChR antikor seviyelerini ve pro-inflamatuar sitokin seviyelerini azalttığı ve böylece Myastenia Gravisin progresresyonunu durdurduğu bildirilmiş.[201] Yine benzer şekilde başka bir çalışmacı deneysel otoimmün myastenia gravisli farelerde CD80 ve CD86 seviyelerini azalttığı ve klinik bulguları baskıladığı belirtilmiş.[202] Yapılan çalışmalar eksozomların Myastenia Gravis için alternatif bir tedavi yöntemi olarak immünsüpresyon potansiyelini göstermektedir. Bununla birlikte, terapötik prosedürleri, klinik etkinliği ve güvenliği belirlemek için daha fazla çalışmaya gereksinim vardır.[200]

Sonuç olarak; kök hücre kaynaklı ekozosomun, sitokinler, kemokinler, büyüme faktörleri, anti-enflamatuar faktörler içermesi ve kök hücre ile aynı terapötik etkiyi göstermesi nedeniyle kök hücre tedavisine alternatif olarak kullanılmaktadır.[203] Kök hücreye göre eksozomların korunması ve üretilmesi daha kolaydır.[204] İntravenöz uygulama kök hücreye göre daha güvenli ve toksik değildir.[205,206] Bununla birlikte, vezikülleri daha iyi karakterize ve standartize etmek ve yeni tedavi stratejileri geliştirmek için daha ileri çalışmalara gereksinim vardır.[42]

KAYNAKLAR

1. Colombo M, Raposo G, Théry C. Biogenesis, secretion, and intercellular interactions of exosomes and other extracellular vesicles. Annu Rev Cell Dev Biol. 2014;30:255-289.
2. Lener T, Gimona M, Aigner L, et al. Applying extracellular vesicles based therapeutics in clinical trials - an ISEV position paper. J Extracell Vesicles. 2015;4:30087.
3. Skotland T, Hessvik NP, Sandvig K, et al. Exosomal lipid composition and the role of ether lipids and phosphoinositides in exosome biology. J Lipid Res. 2019;60(1):9-18.
4. Fitzner D, Schnaars M, van Rossum D, et al. Selective transfer of exosomes from oligodendrocytes to microglia by macropinocytosis. J Cell Sci. 2011;124(Pt 3):447-458.

5. Skotland T, Sagini K, Sandvig K, et al. An emerging focus on lipids in extracellular vesicles. Adv Drug Deliv Rev. 2020;159:308-321.
6. Ohno S, Ishikawa A, Kuroda M. Roles of exosomes and microvesicles in disease pathogenesis. Adv Drug Deliv Rev. 2013;65(3):398-401.
7. Raposo G, Stoorvogel W. Extracellular vesicles: exosomes, microvesicles, and friends. J Cell Biol. 2013;200(4):373-383.
8. Chaput N, Théry C. Exosomes: immune properties and potential clinical implementations. Semin Immunopathol. 2011;33(5):419-440.
9. Lai RC, Tan SS, Teh BJ, et al. Proteolytic Potential of the MSC Exosome Proteome: Implications for an Exosome-Mediated Delivery of Therapeutic Proteasome. Int J Proteomics. 2012;2012:971907.
10. T LR, Sánchez-Abarca LI, Muntión S, et al. MSC surface markers (CD44, CD73, and CD90) can identify human MSC-derived extracellular vesicles by conventional flow cytometry. Cell Commun Signal. 2016;14:2.
11. Ratajczak J, Miekus K, Kucia M, et al. Embryonic stem cell-derived microvesicles reprogram hematopoietic progenitors: evidence for horizontal transfer of mRNA and protein delivery. Leukemia. 2006;20(5):847-856.
12. Valadi H, Ekström K, Bossios A, et al. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. Nature cell biology. 2007;9(6):654-659.
13. Kahlert C, Melo SA, Protopopov A, et al. Identification of double-stranded genomic DNA spanning all chromosomes with mutated KRAS and p53 DNA in the serum exosomes of patients with pancreatic cancer. J Biol Chem. 2014;289(7):3869-3875.
14. Sansone P, Savini C, Kurelac I, et al. Packaging and transfer of mitochondrial DNA via exosomes regulate escape from dormancy in hormonal therapy-resistant breast cancer. Proc Natl Acad Sci U S A. 2017;114(43):E9066-e9075.
15. Kim HS, Choi DY, Yun SJ, et al. Proteomic analysis of microvesicles derived from human mesenchymal stem cells. J Proteome Res. 2012;11(2):839-849.
16. Ferguson SW, Wang J, Lee CJ, et al. The microRNA regulatory landscape of MSC-derived exosomes: a systems view. Sci Rep. 2018;8(1):1419.
17. Yuan O, Lin C, Wagner J, et al. Exosomes Derived from Human Primed Mesenchymal Stem Cells Induce Mitosis and Potentiate Growth Factor Secretion. Stem Cells Dev. 2019;28(6):398-409.
18. Eiró N, Sendon-Lago J, Seoane S, et al. Potential therapeutic effect of the secretome from human uterine cervical stem cells against both cancer and stromal cells compared with adipose tissue stem cells. Oncotarget. 2014;5(21):10692-10708.
19. Bermudez MA, Sendon-Lago J, Eiro N, et al. Corneal epithelial wound healing and bactericidal effect of conditioned medium from human uterine cervical stem cells. Invest Ophthalmol Vis Sci. 2015;56(2):983-992.
20. Bermudez MA, Sendon-Lago J, Seoane S, et al. Anti-inflammatory effect of conditioned medium from human uterine cervical stem cells in uveitis. Exp Eye Res. 2016;149:84-92.
21. Barreca MM, Cancemi P, Geraci F. Mesenchymal and Induced Pluripotent Stem Cells-Derived Extracellular Vesicles: The New Frontier for Regenerative Medicine? Cells. 2020;9(5).
22. Drommelschmidt K, Serdar M, Bendix I, et al. Mesenchymal stem cell-derived extracellular vesicles ameliorate inflammation-induced preterm brain injury. Brain Behav Immun. 2017;60:220-232.
23. Nakano M, Nagaishi K, Konari N, et al. Bone marrow-derived mesenchymal stem cells improve diabetes-induced cognitive impairment by exosome transfer into damaged neurons and astrocytes. Sci Rep. 2016;6:24805.
24. Rani S, Ryan AE, Griffin MD, et al. Mesenchymal Stem Cell-derived Extracellular Vesicles: Toward Cell-free Therapeutic Applications. Mol Ther. 2015;23(5):812-823.
25. Liew LC, Katsuda T, Gailhouste L, et al. Mesenchymal stem cell-derived extracellular vesicles: a glimmer of hope in treating Alzheimer's disease. Int Immunol. 2017;29(1):11-19.
26. Börger V, Bremer M, Ferrer-Tur R, et al. Mesenchymal Stem/Stromal Cell-Derived Extracellular Vesicles and Their Potential as Novel Immunomodulatory Therapeutic Agents. Int J Mol Sci. 2017;18(7).
27. Jung JW, Kwon M, Choi JC, et al. Familial occurrence of pulmonary embolism after intravenous, adipose tissue-derived stem cell therapy. Yonsei Med J. 2013;54(5):1293-1296.
28. Zhang K, Cheng K. Stem cell-derived exosome versus stem cell therapy. Nat Rev Bioeng. 2023:1-2.
29. Anisimov SV, Morizane A, Correia AS. Risks and mechanisms of oncological disease following stem cell transplantation. Stem Cell Rev Rep. 2010;6(3):411-424.
30. Prado NO, Lalli LA, Blanes L, et al. Lyophilization of Molecular Biology Reactions: A Review. Mini Rev Med Chem. 2023;23(4):480-496.
31. Zhang F, Lu Y, Wang M, et al. 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 Probes. 2020;51:101513.
32. Ghasempour E, Hesami S, Movahed E, et al. Mesenchymal stem cell-derived exosomes as a new therapeutic strategy in the brain tumors. Stem Cell Res Ther. 2022;13(1):527.
33. Zhang Y, Bi J, Huang J, et al. Exosome: a review of its classification, isolation techniques, storage, diagnostic and targeted therapy applications. International journal of nanomedicine. 2020:6917-6934.
34. Li T, Yan Y, Wang B, et al. Exosomes derived from human umbilical cord mesenchymal stem cells alleviate liver fibrosis. Stem Cells Dev. 2013;22(6):845-854.
35. Lou G, Chen Z, Zheng M, et al. Mesenchymal stem cell-derived exosomes as a new therapeutic strategy for liver diseases. Exp Mol Med. 2017;49(6):e346.
36. Reis LA, Borges FT, Simões MJ, et al. Bone marrow-de-

rived mesenchymal stem cells repaired but did not prevent gentamicin-induced acute kidney injury through paracrine effects in rats. PLoS One. 2012;7(9):e44092.
37. Grange C, Tapparo M, Bruno S, et al. Biodistribution of mesenchymal stem cell-derived extracellular vesicles in a model of acute kidney injury monitored by optical imaging. Int J Mol Med. 2014;33(5):1055-1063.
38. Tapparo M, Bruno S, Collino F, et al. Renal Regenerative Potential of Extracellular Vesicles Derived from miRNA-Engineered Mesenchymal Stromal Cells. Int J Mol Sci. 2019;20(10).
39. Jiang ZZ, Liu YM, Niu X, et al. Exosomes secreted by human urine-derived stem cells could prevent kidney complications from type I diabetes in rats. Stem Cell Res Ther. 2016;7:24.
40. Birtwistle L, Chen XM, Pollock C. Mesenchymal Stem Cell-Derived Extracellular Vesicles to the Rescue of Renal Injury. Int J Mol Sci. 2021;22(12).
41. Nassar W, El-Ansary M, Sabry D, et al. Umbilical cord mesenchymal stem cells derived extracellular vesicles can safely ameliorate the progression of chronic kidney diseases. Biomater Res. 2016;20:21.
42. Eleuteri S, Fierabracci A. Insights into the Secretome of Mesenchymal Stem Cells and Its Potential Applications. Int J Mol Sci. 2019;20(18).
43. Bagno L, Hatzistergos KE, Balkan W, et al. Mesenchymal Stem Cell-Based Therapy for Cardiovascular Disease: Progress and Challenges. Mol Ther. 2018;26(7):1610-1623.
44. Wang Z, Popowski KD, Zhu D, et al. Exosomes decorated with a recombinant SARS-CoV-2 receptor-binding domain as an inhalable COVID-19 vaccine. Nat Biomed Eng. 2022;6(7):791-805.
45. Ma J, Yong L, Lei P, et al. Advances in microRNA from adipose-derived mesenchymal stem cell-derived exosome: focusing on wound healing. J Mater Chem B. 2022;10(46):9565-9577.
46. Casado-Díaz A, Quesada-Gómez JM, Dorado G. Extracellular Vesicles Derived From Mesenchymal Stem Cells (MSC) in Regenerative Medicine: Applications in Skin Wound Healing. Front Bioeng Biotechnol. 2020;8:146.
47. Bojanic C, To K, Hatoum A, et al. Mesenchymal stem cell therapy in hypertrophic and keloid scars. Cell Tissue Res. 2021;383(3):915-930.
48. Naji A, Eitoku M, Favier B, et al. Biological functions of mesenchymal stem cells and clinical implications. Cell Mol Life Sci. 2019;76(17):3323-3348.
49. Sun Y, Shi H, Yin S, et al. Human mesenchymal stem cell derived exosomes alleviate type 2 diabetes mellitus by reversing peripheral insulin resistance and relieving β-cell destruction. ACS nano. 2018;12(8):7613-7628.
50. Cui Y, Liu C, Huang L, et al. Protective effects of intravitreal administration of mesenchymal stem cell-derived exosomes in an experimental model of optic nerve injury. Exp Cell Res. 2021;407(1):112792.
51. Yu B, Li XR, Zhang XM. Mesenchymal stem cell-derived extracellular vesicles as a new therapeutic strategy for ocular diseases. World J Stem Cells. 2020;12(3):178-187.
52. Shigemoto-Kuroda T, Oh JY, Kim DK, et al. MSC-derived Extracellular Vesicles Attenuate Immune Responses in Two Autoimmune Murine Models: Type 1 Diabetes and Uveoretinitis. Stem Cell Reports. 2017;8(5):1214-1225.
53. Nakano M, Fujimiya M. Potential effects of mesenchymal stem cell derived extracellular vesicles and exosomal miRNAs in neurological disorders. Neural Regen Res. 2021;16(12):2359-2366.
54. Shariati A, Nemati R, Sadeghipour Y, et al. Mesenchymal stromal cells (MSCs) for neurodegenerative disease: A promising frontier. Eur J Cell Biol. 2020;99(6):151097.
55. Marofi F, Hassanzadeh A, Solali S, et al. Epigenetic mechanisms are behind the regulation of the key genes associated with the osteoblastic differentiation of the mesenchymal stem cells: The role of zoledronic acid on tuning the epigenetic changes. Journal of cellular physiology. 2019;234(9):15108-15122.
56. Tavakoli S, Ghaderi Jafarbeigloo HR, Shariati A, et al. Mesenchymal stromal cells; a new horizon in regenerative medicine. Journal of cellular physiology. 2020;235(12):9185-9210.
57. Krstic D, Knuesel I. Deciphering the mechanism underlying late-onset Alzheimer disease. Nat Rev Neurol. 2013;9(1):25-34.
58. Trejo-Lopez JA, Yachnis AT, Prokop S. Neuropathology of Alzheimer's disease. Neurotherapeutics. 2021:1-13.
59. Cone AS, Yuan X, Sun L, et al. Mesenchymal stem cell-derived extracellular vesicles ameliorate Alzheimer's disease-like phenotypes in a preclinical mouse model. Theranostics. 2021;11(17):8129-8142.
60. Zhdanova DY, Poltavtseva RA, Svirshchevskaya EV, et al. Effect of Intranasal Administration of Multipotent Mesenchymal Stromal Cell Exosomes on Memory of Mice in Alzheimer's Disease Model. Bull Exp Biol Med. 2021;170(4):575-582.
61. Cui GH, Wu J, Mou FF, et al. Exosomes derived from hypoxia-preconditioned mesenchymal stromal cells ameliorate cognitive decline by rescuing synaptic dysfunction and regulating inflammatory responses in APP/PS1 mice. Faseb j. 2018;32(2):654-668.
62. Losurdo M, Pedrazzoli M, D'Agostino C, et al. Intranasal delivery of mesenchymal stem cell-derived extracellular vesicles exerts immunomodulatory and neuroprotective effects in a 3xTg model of Alzheimer's disease. Stem Cells Transl Med. 2020;9(9):1068-1084.
63. Ding M, Shen Y, Wang P, et al. Exosomes Isolated From Human Umbilical Cord Mesenchymal Stem Cells Alleviate Neuroinflammation and Reduce Amyloid-Beta Deposition by Modulating Microglial Activation in Alzheimer's Disease. Neurochem Res. 2018;43(11):2165-2177.
64. Chen Y-A, Lu C-H, Ke C-C, et al. Mesenchymal stem cell-derived exosomes ameliorate Alzheimer's disease pathology and improve cognitive deficits. Biomedicines. 2021;9(6):594.
65. Eren E, Leoutsakos JM, Troncoso J, et al. Neuronal-Derived EV Biomarkers Track Cognitive Decline in Alzheimer's Disease. Cells. 2022;11(3).
66. Gao LL, Wu T. The study of brain functional conne-

ctivity in Parkinson's disease. Transl Neurodegener. 2016;5:18.
67. Pagonabarraga J, Kulisevsky J, Strafella AP, et al. Apathy in Parkinson's disease: clinical features, neural substrates, diagnosis, and treatment. The Lancet Neurology. 2015;14(5):518-531.
68. Teixeira FG, Carvalho MM, Panchalingam KM, et al. Impact of the Secretome of Human Mesenchymal Stem Cells on Brain Structure and Animal Behavior in a Rat Model of Parkinson's Disease. Stem Cells Transl Med. 2017;6(2):634-646.
69. Xin H, Li Y, Buller B, et al. Exosome-mediated transfer of miR-133b from multipotent mesenchymal stromal cells to neural cells contributes to neurite outgrowth. Stem Cells. 2012;30(7):1556-1564.
70. Teixeira FG, Panchalingam KM, Assunção-Silva R, et al. Modulation of the mesenchymal stem cell secretome using computer-controlled bioreactors: impact on neuronal cell proliferation, survival and differentiation. Scientific reports. 2016;6(1):27791.
71. Pires AO, Mendes-Pinheiro B, Teixeira FG, et al. Unveiling the Differences of Secretome of Human Bone Marrow Mesenchymal Stem Cells, Adipose Tissue-Derived Stem Cells, and Human Umbilical Cord Perivascular Cells: A Proteomic Analysis. Stem Cells Dev. 2016;25(14):1073-1083.
72. Van Es MA, Hardiman O, Chio A, et al. Amyotrophic lateral sclerosis. The Lancet. 2017;390(10107):2084-2098.
73. Cividini C, Basaia S, Spinelli EG, et al. Amyotrophic Lateral Sclerosis-Frontotemporal Dementia: Shared and Divergent Neural Correlates Across the Clinical Spectrum. Neurology. 2021;98(4):e402-415.
74. Miller TM, Cudkowicz ME, Genge A, et al. Trial of antisense oligonucleotide tofersen for SOD1 ALS. New England Journal of Medicine. 2022;387(12):1099-1110.
75. Méndez-López I, Sancho-Bielsa FJ, Engel T, et al. Progressive mitochondrial SOD1G93A accumulation causes severe structural, metabolic and functional aberrations through OPA1 down-regulation in a mouse model of amyotrophic lateral sclerosis. International Journal of Molecular Sciences. 2021;22(15):8194.
76. Ohta Y, Yamashita T, Nomura E, et al. Improvement of a decreased anti-oxidative activity by edaravone in amyotrophic lateral sclerosis patients. Journal of the neurological sciences. 2020;415:116906.
77. Matthews DC, Mao X, Dowd K, et al. Riluzole, a glutamate modulator, slows cerebral glucose metabolism decline in patients with Alzheimer's disease. Brain. 2021;144(12):3742-3755.
78. Rosen DR, Siddique T, Patterson D, et al. Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. Nature. 1993;362(6415):59-62.
79. Bonafede R, Brandi J, Manfredi M, et al. The anti-apoptotic effect of ASC-exosomes in an in vitro ALS model and their proteomic analysis. Cells. 2019;8(9):1087.
80. Bonafede R, Turano E, Scambi I, et al. ASC-exosomes ameliorate the disease progression in SOD1 (G93A) murine model underlining their potential therapeutic use in human ALS. International journal of molecular sciences. 2020;21(10):3651.
81. Giunti D, Marini C, Parodi B, et al. Role of miRNAs shuttled by mesenchymal stem cell-derived small extracellular vesicles in modulating neuroinflammation. Scientific Reports. 2021;11(1):1740.
82. DSM-5. "Autism spectrum disorder. Diagnostic and Statistical Manual of Mental Disorders (The American Psychiatric Association). 2013:50-59.
83. Mijatovic T, Siniscalco D, Subramanian K, et al. Biomedical approach in autism spectrum disorders-the importance of assessing inflammation. 2018.
84. Gottfried C, Bambini-Junior V, Francis F, et al. The impact of neuroimmune alterations in autism spectrum disorder. Frontiers in psychiatry. 2015;6:121.
85. Perets N, Hertz S, London M, et al. Intranasal administration of exosomes derived from mesenchymal stem cells ameliorates autistic-like behaviors of BTBR mice. Molecular autism. 2018;9:1-12.
86. Moore D, Meays BM, Madduri LSV, et al. Downregulation of an Evolutionary Young miR-1290 in an iPSC-Derived Neural Stem Cell Model of Autism Spectrum Disorder. Stem Cells Int. 2019;2019:8710180.
87. Dendrou CA, Fugger L, Friese MA. Immunopathology of multiple sclerosis. Nat Rev Immunol. 2015;15(9):545-558.
88. Subhramanyam CS, Wang C, Hu Q, et al. Microglia-mediated neuroinflammation in neurodegenerative diseases. Semin Cell Dev Biol. 2019;94:112-120.
89. Chu F, Shi M, Zheng C, et al. The roles of macrophages and microglia in multiple sclerosis and experimental autoimmune encephalomyelitis. J Neuroimmunol. 2018;318:1-7.
90. Li Z, Liu F, He X, et al. Exosomes derived from mesenchymal stem cells attenuate inflammation and demyelination of the central nervous system in EAE rats by regulating the polarization of microglia. Int Immunopharmacol. 2019;67:268-280.
91. Shin T, Ahn M, Kim J, et al. Visual Dysfunction in Multiple Sclerosis and its Animal Model, Experimental Autoimmune Encephalomyelitis: a Review. Mol Neurobiol. 2021;58(7):3484-3493.
92. Kale N. Optic neuritis as an early sign of multiple sclerosis. Eye Brain. 2016;8:195-202.
93. Prüss H. Autoantibodies in neurological disease. Nat Rev Immunol. 2021;21(12):798-813.
94. Lackland DT, Roccella EJ, Deutsch AF, et al. Factors influencing the decline in stroke mortality: a statement from the American Heart Association/American Stroke Association. Stroke. 2014;45(1):315-353.
95. Zhang ZG, Buller B, Chopp M. Exosomes—beyond stem cells for restorative therapy in stroke and neurological injury. Nature Reviews Neurology. 2019;15(4):193-203.
96. Lo EH, Dalkara T, Moskowitz MA. Mechanisms, challenges and opportunities in stroke. Nature reviews neuroscience. 2003;4(5):399-414.
97. Chen K-H, Chen C-H, Wallace CG, et al. Intravenous

administration of xenogenic adipose-derived mesenchymal stem cells (ADMSC) and ADMSC-derived exosomes markedly reduced brain infarct volume and preserved neurological function in rat after acute ischemic stroke. Oncotarget. 2016;7(46):74537.
98. Nalamolu KR, Venkatesh I, Mohandass A, et al. Exosomes treatment mitigates ischemic brain damage but does not improve post-stroke neurological outcome. Cellular physiology and biochemistry: international journal of experimental cellular physiology, biochemistry, and pharmacology. 2019;52(6):1280.
99. Jiang M, Wang H, Jin M, et al. Exosomes from MiR-30d-5p-ADSCs reverse acute ischemic stroke-induced, autophagy-mediated brain injury by promoting M2 microglial/macrophage polarization. Cellular Physiology and Biochemistry. 2018;47(2):864-878.
100. Dabrowska S, Andrzejewska A, Strzemecki D, et al. Human bone marrow mesenchymal stem cell-derived extracellular vesicles attenuate neuroinflammation evoked by focal brain injury in rats. J Neuroinflammation. 2019;16(1):216.
101. Datta A, Chen CP, Sze SK. Discovery of prognostic biomarker candidates of lacunar infarction by quantitative proteomics of microvesicles enriched plasma. PLoS One. 2014;9(4):e94663.
102. Otero-Ortega L, Laso-García F, Gómez-de Frutos M, et al. Role of Exosomes as a Treatment and Potential Biomarker for Stroke. Transl Stroke Res. 2019;10(3):241-249.
103. Gao B, Zhou S, Sun C, et al. Brain Endothelial Cell-Derived Exosomes Induce Neuroplasticity in Rats with Ischemia/Reperfusion Injury. ACS Chem Neurosci. 2020;11(15):2201-2213.
104. Xin H, Li Y, Cui Y, et al. Systemic administration of exosomes released from mesenchymal stromal cells promote functional recovery and neurovascular plasticity after stroke in rats. J Cereb Blood Flow Metab. 2013;33(11):1711-1715.
105. Galgano M, Toshkezi G, Qiu X, et al. Traumatic Brain Injury: Current Treatment Strategies and Future Endeavors. Cell Transplant. 2017;26(7):1118-1130.
106. Capizzi A, Woo J, Verduzco-Gutierrez M. Traumatic brain injury: an overview of epidemiology, pathophysiology, and medical management. Medical Clinics. 2020;104(2):213-238.
107. Kaur P, Sharma S. Recent advances in pathophysiology of traumatic brain injury. Current neuropharmacology. 2018;16(8):1224-1238.
108. Ding D-C, Chang Y-H, Shyu W-C, et al. Human umbilical cord mesenchymal stem cells: a new era for stem cell therapy. Cell transplantation. 2015;24(3):339-347.
109. Chen KH, Shao PL, Li YC, et al. Human Umbilical Cord-Derived Mesenchymal Stem Cell Therapy Effectively Protected the Brain Architecture and Neurological Function in Rat After Acute Traumatic Brain Injury. Cell Transplant. 2020;29:963689720929313.
110. Zhang Y, Chopp M, Meng Y, et al. Effect of exosomes derived from multipluripotent mesenchymal stromal cells on functional recovery and neurovascular plasticity in rats after traumatic brain injury. J Neurosurg. 2015;122(4):856-867.
111. Wang J, Hou Y, Zhang L, et al. Estrogen attenuates traumatic brain injury by inhibiting the activation of microglia and astrocyte-mediated neuroinflammatory responses. Molecular neurobiology. 2021;58:1052-1061.
112. Cui L, Luo W, Jiang W, et al. Human umbilical cord mesenchymal stem cell-derived exosomes promote neurological function recovery in rat after traumatic brain injury by inhibiting the activation of microglia and astrocyte. Regen Ther. 2022;21:282-287.
113. Ahuja CS, Wilson JR, Nori S, et al. Traumatic spinal cord injury. Nat Rev Dis Primers. 2017;3:17018.
114. Gordon S. Alternative activation of macrophages. Nature reviews immunology. 2003;3(1):23-35.
115. Mantovani A, Sica A, Sozzani S, et al. The chemokine system in diverse forms of macrophage activation and polarization. Trends in immunology. 2004;25(12):677-686.
116. David S, Kroner A. Repertoire of microglial and macrophage responses after spinal cord injury. Nature Reviews Neuroscience. 2011;12(7):388-399.
117. Sun G, Li G, Li D, et al. hucMSC derived exosomes promote functional recovery in spinal cord injury mice via attenuating inflammation. Materials Science and Engineering: C. 2018;89:194-204.
118. Liu W-z, Ma Z-j, Li J-r, et al. Mesenchymal stem cell-derived exosomes: therapeutic opportunities and challenges for spinal cord injury. Stem cell research & therapy. 2021;12(1):1-15.
119. Liang ZY, Xu XJ, Rao J, et al. Mesenchymal Stem Cell-Derived Exosomal MiRNAs Promote M2 Macrophages Polarization: Therapeutic Opportunities for Spinal Cord Injury. Front Mol Neurosci. 2022;15:926928.
120. Carvalho CR, Oliveira JM, Reis RL. Modern Trends for Peripheral Nerve Repair and Regeneration: Beyond the Hollow Nerve Guidance Conduit. Front Bioeng Biotechnol. 2019;7:337.
121. Nocera G, Jacob C. Mechanisms of Schwann cell plasticity involved in peripheral nerve repair after injury. Cell Mol Life Sci. 2020;77(20):3977-3989.
122. Lopez-Leal R, Court FA. Schwann Cell Exosomes Mediate Neuron-Glia Communication and Enhance Axonal Regeneration. Cell Mol Neurobiol. 2016;36(3):429-436.
123. Yu T, Xu Y, Ahmad MA, et al. Exosomes as a Promising Therapeutic Strategy for Peripheral Nerve Injury. Curr Neuropharmacol. 2021;19(12):2141-2151.
124. Bucan V, Vaslaitis D, Peck CT, et al. Effect of Exosomes from Rat Adipose-Derived Mesenchymal Stem Cells on Neurite Outgrowth and Sciatic Nerve Regeneration After Crush Injury. Mol Neurobiol. 2019;56(3):1812-1824.
125. Zhao J, Ding Y, He R, et al. Dose-effect relationship and molecular mechanism by which BMSC-derived exosomes promote peripheral nerve regeneration after crush injury. Stem Cell Res Ther. 2020;11(1):360.
126. Hobson MI, Green CJ, Terenghi G. VEGF enhances intraneural angiogenesis and improves nerve regeneration after axotomy. J Anat. 2000;197 Pt 4(Pt 4):591-605.
127. Zhang B, Wu X, Zhang X, et al. Human umbilical cord

mesenchymal stem cell exosomes enhance angiogenesis through the Wnt4/β-catenin pathway. Stem Cells Transl Med. 2015;4(5):513-522.
128. Bian S, Zhang L, Duan L, et al. Extracellular vesicles derived from human bone marrow mesenchymal stem cells promote angiogenesis in a rat myocardial infarction model. J Mol Med (Berl). 2014;92(4):387-397.
129. Pascucci L, Alessandri G, Dall'Aglio C, et al. Membrane vesicles mediate pro-angiogenic activity of equine adipose-derived mesenchymal stromal cells. Vet J. 2014;202(2):361-366.
130. Rotshenker S. Wallerian degeneration: the innate-immune response to traumatic nerve injury. J Neuroinflammation. 2011;8:109.
131. Toh WS, Zhang B, Lai RC, et al. Immune regulatory targets of mesenchymal stromal cell exosomes/small extracellular vesicles in tissue regeneration. Cytotherapy. 2018;20(12):1419-1426.
132. Sun G, Li G, Li D, et al. hucMSC derived exosomes promote functional recovery in spinal cord injury mice via attenuating inflammation. Mater Sci Eng C Mater Biol Appl. 2018;89:194-204.
133. Wei Z, Fan B, Ding H, et al. Proteomics analysis of Schwann cell-derived exosomes: a novel therapeutic strategy for central nervous system injury. Mol Cell Biochem. 2019;457(1-2):51-59.
134. Fleiss B, Tann CJ, Degos V, et al. Inflammation-induced sensitization of the brain in term infants. Developmental Medicine & Child Neurology. 2015;57:17-28.
135. Jellema RK, Wolfs TG, Lima Passos V, et al. Mesenchymal stem cells induce T-cell tolerance and protect the preterm brain after global hypoxia-ischemia. PLoS One. 2013;8(8):e73031.
136. Ophelders DR, Wolfs TG, Jellema RK, et al. Mesenchymal Stromal Cell-Derived Extracellular Vesicles Protect the Fetal Brain After Hypoxia-Ischemia. Stem Cells Transl Med. 2016;5(6):754-763.
137. Chen J, Liu Z, Hong MM, et al. Proangiogenic compositions of microvesicles derived from human umbilical cord mesenchymal stem cells. PLoS One. 2014;9(12):e115316.
138. Sisa C, Kholia S, Naylor J, et al. Mesenchymal stromal cell derived extracellular vesicles reduce hypoxia-ischaemia induced perinatal brain injury. Frontiers in physiology. 2019;10:282.
139. Colver A, Fairhurst C, Pharoah PO. Cerebral palsy. Lancet. 2014;383(9924):1240-1249.
140. Rosenbaum P, Paneth N, Leviton A, et al. A report: the definition and classification of cerebral palsy April 2006. Dev Med Child Neurol Suppl. 2007;109:8-14.
141. Huang L, Zhang L. Neural stem cell therapies and hypoxic-ischemic brain injury. Prog Neurobiol. 2019;173:1-17.
142. Nguyen LT, Nguyen AT, Vu CD, et al. Outcomes of autologous bone marrow mononuclear cells for cerebral palsy: an open label uncontrolled clinical trial. BMC Pediatr. 2017;17(1):104.
143. Mancías-Guerra C, Marroquín-Escamilla AR, González-Llano O, et al. Safety and tolerability of intrathecal delivery of autologous bone marrow nucleated cells in children with cerebral palsy: an open-label phase I trial. Cytotherapy. 2014;16(6):810-820.
144. Sharma A, Sane H, Gokulchandran N, et al. A clinical study of autologous bone marrow mononuclear cells for cerebral palsy patients: a new frontier. Stem Cells Int. 2015;2015:905874.
145. Zali A, Arab L, Ashrafi F, et al. Intrathecal injection of CD133-positive enriched bone marrow progenitor cells in children with cerebral palsy: feasibility and safety. Cytotherapy. 2015;17(2):232-241.
146. Pastores GM. Lysosomal storage disorders: Clinical and therapeutic aspects. Handb Clin Neurol. 2023;196:557-567.
147. Vitner EB, Platt FM, Futerman AH. Common and Uncommon Pathogenic Cascades in Lysosomal Storage Diseases*. Journal of Biological Chemistry. 2010;285(27):20423-20427.
148. Vitner EB, Platt FM, Futerman AH. Common and uncommon pathogenic cascades in lysosomal storage diseases. Journal of Biological Chemistry. 2010;285(27):20423-20427.
149. Wenger DA, Coppola S, Liu S-L. Insights into the diagnosis and treatment of lysosomal storage diseases. Archives of neurology. 2003;60(3):322-328.
150. Hollak CE, Wijburg FA. Treatment of lysosomal storage disorders: successes and challenges. Journal of inherited metabolic disease. 2014;37:587-598.
151. Gleason AM, Woo EG, McKinney C, et al. The role of exosomes in lysosomal storage disorders. Biomolecules. 2021;11(4):576.
152. Do MA, Levy D, Brown A, et al. Targeted delivery of lysosomal enzymes to the endocytic compartment in human cells using engineered extracellular vesicles. Scientific reports. 2019;9(1):17274.
153. Lu B, Ku J, Flojo R, et al. Exosome- and extracellular vesicle-based approaches for the treatment of lysosomal storage disorders. Adv Drug Deliv Rev. 2022;188:114465.
154. Abasolo I, Seras-Franzoso J, Moltó-Abad M, et al. Nanotechnology-based approaches for treating lysosomal storage disorders, a focus on Fabry disease. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology. 2021;13(3):e1684.
155. Valstar MJ, Ruijter GJ, van Diggelen OP, et al. Sanfilippo syndrome: a mini-review. J Inherit Metab Dis. 2008;31(2):240-252.
156. Seras-Franzoso J, Díaz-Riascos ZV, Corchero JL, et al. Extracellular vesicles from recombinant cell factories improve the activity and efficacy of enzymes defective in lysosomal storage disorders. Journal of extracellular vesicles. 2021;10(5):e12058.
157. Flanagan M, Pathak I, Gan Q, et al. Umbilical mesenchymal stem cell-derived extracellular vesicles as enzyme delivery vehicle to treat Morquio A fibroblasts. Stem Cell Research & Therapy. 2021;12(1):1-15.
158. Coulson-Thomas VJ, Caterson B, Kao WW-Y. Transplantation of human umbilical mesenchymal stem cells cures the corneal defects of mucopolysaccharidosis VII mice. Stem Cells. 2013;31(10):2116-2126.

159. Town M, Jean G, Cherqui S, et al. A novel gene encoding an integral membrane protein is mutated in nephropathic cystinosis. Nature genetics. 1998;18(4):319-324.
160. Syres K, Harrison F, Tadlock M, et al. Successful treatment of the murine model of cystinosis using bone marrow cell transplantation. Blood, The Journal of the American Society of Hematology. 2009;114(12):2542-2552.
161. Iglesias DM, El-Kares R, Taranta A, et al. Stem cell microvesicles transfer cystinosin to human cystinotic cells and reduce cystine accumulation in vitro. 2012.
162. Chang T-Y, Reid PC, Sugii S, et al. Niemann-Pick type C disease and intracellular cholesterol trafficking. Journal of Biological Chemistry. 2005;280(22):20917-20920.
163. Walkley SU, Suzuki K. Consequences of NPC1 and NPC2 loss of function in mammalian neurons. Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids. 2004;1685(1-3):48-62.
164. Sleat DE, Wiseman JA, El-Banna M, et al. Genetic evidence for nonredundant functional cooperativity between NPC1 and NPC2 in lipid transport. Proceedings of the National Academy of Sciences. 2004;101(16):5886-5891.
165. Strauss K, Goebel C, Runz H, et al. Exosome secretion ameliorates lysosomal storage of cholesterol in Niemann-Pick type C disease. J Biol Chem. 2010;285(34):26279-26288.
166. Kohan R, Cismondi IA, Oller-Ramirez AM, et al. Therapeutic approaches to the challenge of neuronal ceroid lipofuscinoses. Curr Pharm Biotechnol. 2011;12(6):867-883.
167. El-Hage N, Haney MJ, Zhao Y, et al. Extracellular Vesicles Released by Genetically Modified Macrophages Activate Autophagy and Produce Potent Neuroprotection in Mouse Model of Lysosomal Storage Disorder, Batten Disease. Cells. 2023;12(11).
168. Iqbal S, Khan MUG, Saba T, et al. Computer-assisted brain tumor type discrimination using magnetic resonance imaging features. Biomed Eng Lett. 2018;8(1):5-28.
169. Park JH, de Lomana ALG, Marzese DM, et al. A Systems Approach to Brain Tumor Treatment. Cancers (Basel). 2021;13(13).
170. Bors LA, Erdő F. Overcoming the blood–brain barrier. challenges and tricks for CNS drug delivery. Scientia Pharmaceutica. 2019;87(1):6.
171. Gerstner ER, Fine RL. Increased permeability of the blood-brain barrier to chemotherapy in metastatic brain tumors: establishing a treatment paradigm. J Clin Oncol. 2007;25(16):2306-2312.
172. Record M, Subra C, Silvente-Poirot S, et al. Exosomes as intercellular signalosomes and pharmacological effectors. Biochem Pharmacol. 2011;81(10):1171-1182.
173. Zhou W, Fong MY, Min Y, et al. Cancer-secreted miR-105 destroys vascular endothelial barriers to promote metastasis. Cancer Cell. 2014;25(4):501-515.
174. Choi JU, Park IK, Lee YK, et al. The Biological Function and Therapeutic Potential of Exosomes in Cancer: Exosomes as Efficient Nanocommunicators for Cancer Therapy. Int J Mol Sci. 2020;21(19).
175. Katakowski M, Buller B, Zheng X, et al. Exosomes from marrow stromal cells expressing miR-146b inhibit glioma growth. Cancer Lett. 2013;335(1):201-204.
176. Altanerova U, Benejova K, Altanerova V, et al. Dental pulp mesenchymal stem/stromal cells labeled with iron sucrose release exosomes and cells applied intra-nasally migrate to intracerebral glioblastoma. Neoplasma. 2016;63(6):925-933.
177. Zhu W, Huang L, Li Y, et al. Exosomes derived from human bone marrow mesenchymal stem cells promote tumor growth in vivo. Cancer Lett. 2012;315(1):28-37.
178. Kolb SJ, Kissel JT. Spinal Muscular Atrophy. Neurol Clin. 2015;33(4):831-846.
179. Lefebvre S, Bürglen L, Reboullet S, et al. Identification and characterization of a spinal muscular atrophy-determining gene. Cell. 1995;80(1):155-165.
180. Munsat TL, Davies KE. International SMA consortium meeting. (26-28 June 1992, Bonn, Germany). Neuromuscul Disord. 1992;2(5-6):423-428.
181. Finkel RS, McDermott MP, Kaufmann P, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. Neurology. 2014;83(9):810-817.
182. Farrar MA, Vucic S, Johnston HM, et al. Pathophysiological insights derived by natural history and motor function of spinal muscular atrophy. J Pediatr. 2013;162(1):155-159.
183. Schorling DC, Pechmann A, Kirschner J. Advances in Treatment of Spinal Muscular Atrophy - New Phenotypes, New Challenges, New Implications for Care. J Neuromuscul Dis. 2020;7(1):1-13.
184. Russman BS. Spinal muscular atrophy: clinical classification and disease heterogeneity. J Child Neurol. 2007;22(8):946-951.
185. Zerres K, Rudnik-Schöneborn S, Forrest E, et al. A collaborative study on the natural history of childhood and juvenile onset proximal spinal muscular atrophy (type II and III SMA): 569 patients. J Neurol Sci. 1997;146(1):67-72.
186. Nash LA, McFall ER, Perozzo AM, et al. Survival Motor Neuron Protein is Released from Cells in Exosomes: A Potential Biomarker for Spinal Muscular Atrophy. Sci Rep. 2017;7(1):13859.
187. Mah JK, Korngut L, Dykeman J, et al. A systematic review and meta-analysis on the epidemiology of Duchenne and Becker muscular dystrophy. Neuromuscul Disord. 2014;24(6):482-491.
188. Lapidos KA, Kakkar R, McNally EM. The dystrophin glycoprotein complex: signaling strength and integrity for the sarcolemma. Circ Res. 2004;94(8):1023-1031.
189. Bentzinger CF, Wang YX, Rudnicki MA. Building muscle: molecular regulation of myogenesis. Cold Spring Harbor perspectives in biology. 2012;4(2):a008342.
190. Dumont NA, Wang YX, Von Maltzahn J, et al. Dystrophin expression in muscle stem cells regulates their polarity and asymmetric division. Nature medicine. 2015;21(12):1455-1463.
191. Keefe AC, Kardon G. A new role for dystrophin in muscle stem cells. Nature medicine. 2015;21(12):1391-1393.
192. Bier A, Berenstein P, Kronfeld N, et al. Placenta-derived

mesenchymal stromal cells and their exosomes exert therapeutic effects in Duchenne muscular dystrophy. Biomaterials. 2018;174:67-78.
193. Zanotti S, Gibertini S, Blasevich F, et al. Exosomes and exosomal miRNAs from muscle-derived fibroblasts promote skeletal muscle fibrosis. Matrix Biol. 2018;74:77-100.
194. Gartz M, Darlington A, Afzal MZ, et al. Exosomes exert cardioprotection in dystrophin-deficient cardiomyocytes via ERK1/2-p38/MAPK signaling. Sci Rep. 2018;8(1):16519.
195. Aminzadeh MA, Rogers RG, Fournier M, et al. Exosome-Mediated Benefits of Cell Therapy in Mouse and Human Models of Duchenne Muscular Dystrophy. Stem Cell Reports. 2018;10(3):942-955.
196. Leng L, Dong X, Gao X, et al. Exosome-mediated improvement in membrane integrity and muscle function in dystrophic mice. Mol Ther. 2021;29(4):1459-1470.
197. Joshua AM, Misri Z. Physiotherapy for Adult Neurological Conditions: Springer 2022.
198. Koneczny I, Herbst R. Myasthenia Gravis: Pathogenic Effects of Autoantibodies on Neuromuscular Architecture. Cells. 2019;8(7).
199. Gilhus NE, Tzartos S, Evoli A, et al. Myasthenia gravis. Nat Rev Dis Primers. 2019;5(1):30.
200. Huang EJ, Wu MH, Wang TJ, et al. Myasthenia Gravis: Novel Findings and Perspectives on Traditional to Regenerative Therapeutic Interventions. Aging Dis. 2023;14(4):1070-1092.
201. Bu N, Wu HQ, Zhang GL, et al. Immature dendritic cell exosomes suppress experimental autoimmune myasthenia gravis. J Neuroimmunol. 2015;285:71-75.
202. Yin W, Ouyang S, Luo Z, et al. Immature Exosomes Derived from MicroRNA-146a Overexpressing Dendritic Cells Act as Antigen-Specific Therapy for Myasthenia Gravis. Inflammation. 2017;40(4):1460-1473.
203. Fierabracci A, Del Fattore A, Muraca M. The Immunoregulatory Activity of Mesenchymal Stem Cells: 'State of Art' and 'Future Avenues'. Curr Med Chem. 2016;23(27):3014-3024.
204. Mardpour S, Hamidieh AA, Taleahmad S, et al. Interaction between mesenchymal stromal cell-derived extracellular vesicles and immune cells by distinct protein content. J Cell Physiol. 2019;234(6):8249-8258.
205. Saleh AF, Lázaro-Ibáñez E, Forsgard MA, et al. Extracellular vesicles induce minimal hepatotoxicity and immunogenicity. Nanoscale. 2019;11(14):6990-7001.
206. Koniusz S, Andrzejewska A, Muraca M, et al. Extracellular Vesicles in Physiology, Pathology, and Therapy of the Immune and Central Nervous System, with Focus on Extracellular Vesicles Derived from Mesenchymal Stem Cells as Therapeutic Tools. Front Cell Neurosci. 2016;10:109.