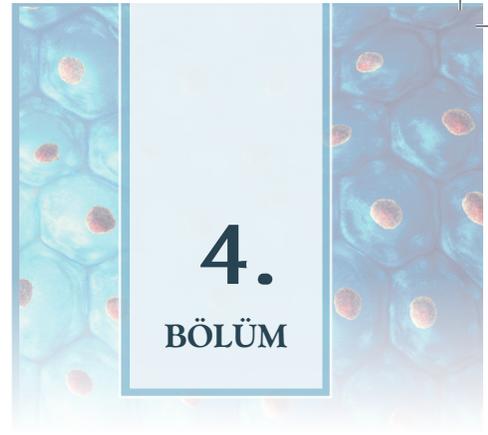


Yağ Dokusu Kökenli Mezenkimal Kök Hücreler ve Uygulama Alanları



Esra ASLAN¹
Çiğdem KARACA²

GİRİŞ

Mezenkimal kök hücreler (MKH'ler), kendi kendini yenileme yeteneğine sahip olan ve aynı zamanda çok soylu farklılaşma sergileyen stromal hücrelerdir. MKH'ler göbek kordonu, endometriyal polipler, adet kanı, kemik iliği, yağ dokusu gibi çeşitli dokulardan izole edilebilir (1). MKH'lerin çok soylu kapasitesi, onları hücre temelli tıbbi tedaviler için oldukça değerli hale getirir (2).

Yağ dokusu ise erişilebilir oluşu, bol miktarda bulunması ve diğer kaynaklara kıyasla daha az ağırlı toplama prosedürüne sahip olması açısından kök hücre kaynaklarının en başında yer alır (3). Yağ dokusu kökenli mezenkimal kök hücreler (AMKH'ler), bağışıklık reaksiyonunu düzenlemek, farklılaşma, göç, enzimatik reaksiyonlar için sinyaller sağlamak ve dengeli doku homeostazının rejeneratif taleplerini dengelemek için organ sistemleri ile iletişime geçer (4). Doku onarımı ve yenilenmesi için etkili hücre temelli tedavilere duyulan ihtiyaç gittikçe artmakta ve pek çok alanda terapötik olarak AMKH'ler denenmektedir. Rejeneratif tıpta klinik uygulamalar için AMKH tedavisi umut vaat eder duruma gelmiştir.

MEZENKİMAL KÖK HÜCRELER

Kemik iliğinde hematopoietik kök hücreler (HKH'ler) ve MKH'ler olmak üzere iki bağımsız yetişkin kök hücre popülasyonu bulunur (5). Osteosit, adiposit

¹ Öğr. Gör. Dr., Afyonkarahisar Sağlık Bilimleri Üniversitesi Tıp Fakültesi Histoloji Embriyoloji AD., dr_esragul@hotmail.com

² Öğr. Gör. Dr., Afyonkarahisar Sağlık Bilimleri Üniversitesi Tıp Fakültesi Histoloji Embriyoloji AD., drc_karaca@hotmail.com

sülin benzeri büyüme faktörü ve VEGF gibi artan nörotrofik faktör seviyeleri ve azalmış apoptotik hücre ölümü tespit edilmiştir (61). Amiloid öncü protein / presenilin 1 (APP / PS1) çift transgenik farelerde uzaysal öğrenme / hafıza yeteneğinin geri kazanılmasında AMKH'lerin intraserebral uygulamasının etkinliği gösterilmiş ve AMKH'lerin, Alzheimer hastalığı ile ilişkili nöropatolojik açıkları iyileştirme kapasitesine sahip rejeneratif tedaviler için umut verici yeni bir hücre kaynağı olduğunu bildirilmiştir (62). Ayrıca, i.v. AMKH uygulamasının, Alzheimer hastalığı fare modellerinde demans semptomları ve terapötik etkileri üzerinde palyatif etkilere sahip olduğu da gösterilmiştir (63).

AMKH'ler yukarıda bahsedilen hastalıklar dışında akut ve kronik Greft Versus Host, çeşitli kalp hastalıkları, spinal kord hasarları, inme, myokard iskemisi, KOAH, idiyopatik pulmoner fibrozis kronik karaciğer yetmezliği akut böbrek hasarı gliom ve glioblastom gibi pekçok farklı hastalıkla denenmiş olup denenmeye devam edilmekte ve yüz güldürücü sonuçlar elde edildiği bildirilmektedir.

SONUÇ

AMKH'ler, diğer hücre tiplerine farklılaşma, büyüme faktörleri ve sitokinleri salgılamaları, anjiyogenezi teşvik etme, apoptozu ve oksidatif stresi azaltma ve yara iyileşme sürecini hızlandırmak gibi önemli potansiyellere sahiptir. Ayrıca bol bulunması, izolasyon kolaylığı ve doku yenilenmesini desteklemek için doğal mekanizmalara sahip oluşu da tercih edilme sebepleri arasındadır. Preklinik ve klinik çalışmalar, bu hücrelerin özellikle dirençli hastalığı olan hastaların mevcut tedavilere ek olarak klinik sonuçları iyileştirebileceğini öne sürmektedir. Rutin klinik kullanımdan önce devam eden araştırmaların insan deneklerdeki güvenliği ve etkinliği kanıtlanmalıdır. Yapılan çalışmaların sayısı giderek artmakta ve elde edilen sonuçlar umut verici görünmektedir.

KAYNAKÇA

1. Ding DC, Shyu WC, Lin SZ. Mesenchymal stem cells. *Cell Transplant*. 2011;20(1):5-14.
2. Mahmoudifar N, Doran PM. Mesenchymal Stem Cells Derived from Human Adipose Tissue. *Methods Mol Biol*. 2015;1340:53-64.
3. Mazini L, Rochette L, Amine M, Malka G. Regenerative Capacity of Adipose Derived Stem Cells (ADSCs), Comparison with Mesenchymal Stem Cells (MSC's). *Int J Mol Sci*. 2019;20(10):2523.
4. Gaur M, Dobke M, Lunyak VV. Mesenchymal Stem Cells from Adipose Tissue in Clinical Applications for Dermatological Indications and Skin Aging. *Int J Mol Sci*. 2017;18(1):208.

5. Caplan AI. Mesenchymal stem cells. *J Orthop Res.* 1991;9(5):641-50.
6. Mundra V, Gerling IC, Mahato RI. Mesenchymal stem cell-based therapy. *Mol Pharm.* 2013;10(1):77-89.
7. Friedenstein AJ, Gorskaja JF, Kulagina NN. Fibroblast precursors in normal and irradiated mouse hematopoietic organs. *Exp Hematol.* 1976; 4(5):267-274.
8. Strioga M, Viswanathan S, Darinskas A, et al. Same or not the same? Comparison of adipose tissue-derived versus bone marrow-derived mesenchymal stem and stromal cells. *Stem Cells Dev.* 2012;21(14):2724-52.
9. Horwitz EM, Le Blanc K, Dominici M, et al. Clarification of the nomenclature for MSC: The International Society for Cellular Therapy position statement. *Cytotherapy.* 2005;7(5):393-5.
10. Dominici M, Le Blanc K, Mueller I, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy* 2006;8(4):315-317.
11. 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.
12. Lu LL, Liu YJ, Yang SG, et al. Isolation and characterization of human umbilical cord mesenchymal stem cells with hematopoiesis-supportive function and other potentials. *Haematologica.* 2006;91(8):1017-1026.
13. da Silva Meirelles L, Chagastelles PC, Nardi NB. Mesenchymal stem cells reside in virtually all post-natal organs and tissues. *Journal of cell science.* 2006;119:2204-2213.
14. Seeberger KL, Dufour JM, Shapiro AM, et al. Expansion of mesenchymal stem cells from human pancreatic ductal epithelium. *Lab Invest.* 2006;86(2):141-53.
15. Perrotta FM, Guerra G, De Socio A, et al. Mesenchymal stem cells: a possible role in the pathogenesis and treatment of spondyloarthritis. *Reumatismo.* 2017;69(1):1-8.
16. Squillaro T, Peluso G, Galderisi U. Clinical Trials With Mesenchymal Stem Cells: An Update. *Cell Transplant.* 2016;25(5):829-48.
17. Galipeau J, Sensébé L. Mesenchymal Stromal Cells: Clinical Challenges and Therapeutic Opportunities. *Cell Stem Cell.* 2018;22(6):824-833.
18. Trounson A, McDonald C. Stem Cell Therapies in Clinical Trials: Progress and Challenges. *Cell Stem Cell.* 2015;17(1):11-22.
19. Wei X, Yang X, Han ZP, et al. Mesenchymal stem cells: a new trend for cell therapy. *Acta Pharmacol Sin.* 2013;34(6):747-54.
20. Dicker A, Le Blanc K, Aström G, et al. Functional studies of mesenchymal stem cells derived from adult human adipose tissue. *Exp Cell Res.* 2005;308(2):283-90.
21. Kokai LE, Marra K, Rubin JP. Adipose stem cells: biology and clinical applications for tissue repair and regeneration. *Translational Research.* 2014;163(4):399-408.
22. Zuk PA, Zhu M, Ashjian P, et al. Human adipose tissue is a source of multipotent stem cells. *Molecular Biology of the Cell.* 2002;13(12):4279-4295.
23. Gimble JM. Adipose tissue-derived therapeutics. *Expert Opin Biol Ther.* 2003;3(5):705-13
24. Van RL, CE Bayliss, DA Roncari. Cytological and enzymological characterization of adult human adipocyte precursors in culture. *J Clin Invest.* 1976;58:699-704.
25. Zuk PA, Zhu M, H Mizuno, et al. Multilineage cells from human adipose tissue: implications for cell-based therapies. *Tissue Eng.* 2001;7:211-228.

26. Varghese J, Griffin M, Mosahebi A, et al. Systematic review of patient factors affecting adipose stem cell viability and function: implications for regenerative therapy. *Stem Cell Res Ther.* 2017;8:45.
27. Fang Y, Zhang Y, Zhou J, et al. Adipose-derived mesenchymal stem cell exosomes: a novel pathway for tissues repair. *Cell Tissue Bank.* 2019;20(2):153-161.
28. Fraser JK, Zhu M, Wulur I, et al. Adipose-derived stem cells. *Methods Mol Biol.* 2008; 449:59-67.
29. Fraser JK, Wulur I, Alfonso Z, et al. Fat tissue: an underappreciated source of stem cells for biotechnology. *Trends Biotechnol.* 2006; 24(4):150-4.
30. Mildmay-White A, Khan W. Cell Surface Markers on Adipose-Derived Stem Cells: A Systematic Review. *Curr Stem Cell Res Ther.* 2017;12(6):484-492.
31. Huang SJ, Fu RH, Shyu WC, et al. Adipose-derived stem cells: isolation, characterization, and differentiation potential. *Cell Transplant.* 2013;22(4):701-9.
32. Noël D, Caton D, Roche S, et al. Cell specific differences between human adipose-derived and mesenchymal-stromal cells despite similar differentiation potentials. *Exp Cell Res.* 2008;314(7):1575-84.
33. Katz AJ, Hedrick MH, Llull R, et al. A novel device for the simple and efficient refinement of liposuctioned tissue. *Plast Reconstr Surg.* 2001; 107(2):595-7
34. Fodor PB, Paulseth SG. Adipose Derived Stromal Cell (ADSC) Injections for Pain Management of Osteoarthritis in the Human Knee Joint. *Aesthet Surg J.* 2016;36:229-36.
35. Roato I, Belisario DC, Compagno M, et al. Concentrated adipose tissue infusion for the treatment of knee osteoarthritis: clinical and histological observations. *Int Orthop.* 2019;43:15-23.
36. Koh YG, Choi YJ, Kwon SK, et al. Clinical results and second-look arthroscopic findings after treatment with adipose-derived stem cells for knee osteoarthritis. *Knee Surg Sports Traumatol Arthrosc.* 2015;23:1308-16.
37. Jo CH, Lee YG, Shin WH, et al. Intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: a proof-of-concept clinical trial. *Stem Cells.* 2014;32:1254-66.
38. Freitag J, Bates D, Wickham J, et al. Adipose-derived mesenchymal stem cell therapy in the treatment of knee osteoarthritis: a randomized controlled trial. *Regen Med.* 2019 Mar;14(3):213-230
39. Li Y, Zhang W, Gao J, et al. Adipose tissue-derived stem cells suppress hypertrophic scar fibrosis via the p38/MAPK signaling pathway. *Stem Cell Res Ther.* 2016;7(1):102.
40. Shingyochi Y, Orbay H, Mizuno H. Adipose-derived stem cells for wound repair and regeneration. *Expert Opin Biol Ther.* 2015;15(9):1285-92.
41. Trottier V, Marceau-Fortier G, Germain L, et al. IFATS collection: Using human adipose-derived stem/stromal cells for the production of new skin substitutes. *Stem Cells.* 2008;26(10):2713-23.
42. Trottier JA, Cherutti G, Motta AC, et al. Bilaminar Device of Poly(Lactic-co-Glycolic Acid)/Collagen Cultured With Adipose-Derived Stem Cells for Dermal Regeneration. *Artif Organs.* 2016;40(10):938-949.
43. Hu L, Wang J, Zhou X, et al. Exosomes derived from human adipose mesenchymal stem cells accelerates cutaneous wound healing via optimizing the characteristics of fibroblasts. *Sci Rep.* 2016;6:32993.

44. Rigotti G, Charles-de-Sá L, Gontijo-de-Amorim NF, et al. Expanded Stem Cells, Stromal-Vascular Fraction, and Platelet-Rich Plasma Enriched Fat: Comparing Results of Different Facial Rejuvenation Approaches in a Clinical Trial. *Aesthet Surg J*. 2016;36(3):261-70.
45. Charles-de-Sá L, Gontijo-de-Amorim NF, Maeda Takiya C, et al. Antiaging treatment of the facial skin by fat graft and adipose-derived stem cells. *Plast Reconstr Surg*. 2015;135(4):999-1009.
46. Wei S, Xie S, Yang Z, et al. Allogeneic adipose-derived stem cells suppress mTORC1 pathway in a murine model of systemic lupus erythematosus. *Lupus*. 2019;28(2):199-209.
47. He X, Zhang Y, Zhu A, et al. Suppression of interleukin 17 contributes to the immunomodulatory effects of adipose-derived stem cells in a murine model of systemic lupus erythematosus. *Immunol Res*. 2016;64(5-6):1157-1167.
48. Panés J, García-Olmo D, Van Assche G, et al. Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn's disease: a phase 3 randomised, double-blind controlled trial. *Lancet*. 2016;388(10051):1281-90.
49. Panés J, García-Olmo D, Van Assche G, et al. Long-term Efficacy and Safety of Stem Cell Therapy (Cx601) for Complex Perianal Fistulas in Patients With Crohn's Disease. *Gastroenterology*. 2018;154(5):1334-1342.e4.
50. Abdallah AN, Shamaa AA, El-Tookhy OS. Evaluation of treatment of experimentally induced canine model of multiple sclerosis using laser activated non-expanded adipose derived stem cells. *Res Vet Sci*. 2019;125:71-81.
51. Klinker MW, Wei CH. Mesenchymal stem cells in the treatment of inflammatory and autoimmune diseases in experimental animal models. *World J Stem Cells*. 2015;7:556-67.
52. Stepien A, Dabrowska NL, Maciagowska M, et al. Clinical Application of Autologous Adipose Stem Cells in Patients with Multiple Sclerosis: Preliminary Results. *Mediators Inflamm*. 2016;2016:5302120.
53. Fernandez O, Izquierdo G, Fernandez V, et al. Adipose-derived mesenchymal stem cells (AdMSC) for the treatment of secondary-progressive multiple sclerosis: A triple blinded, placebo controlled, randomized phase I/II safety and feasibility study. *PLoS One* 2018;13(5):e0195891.
54. Jafarzadeh Bejargafshe M, Hedayati M, Zahabiasli S, et al. Safety and efficacy of stem cell therapy for treatment of neural damage in patients with multiple sclerosis. *Stem Cell Investig*. 2019;6:44.
55. Fang Y, Tian X, Bai S, et al. Autologous transplantation of adipose-derived mesenchymal stem cells ameliorates streptozotocin-induced diabetic nephropathy in rats by inhibiting oxidative stress, pro-inflammatory cytokines and the p38 MAPK signaling pathway. *Int J Mol Med*. 2012;30(1):85-92.
56. Lin G, Wang G, Liu G, et al. Treatment of type 1 diabetes with adipose tissue-derived stem cells expressing pancreatic duodenal homeobox 1. *Stem Cells Dev*. 2009;18(10):1399-406.
57. Vanikar AV, Dave SD, Thakkar UG, et al. Cotransplantation of adipose tissue-derived insulin-secreting mesenchymal stem cells and hematopoietic stem cells: a novel therapy for insulin-dependent diabetes mellitus. *Stem Cells Int*. 2010;2010:582382.

58. Riordan NH, Ichim TE, Min WP, et al. Non-expanded adipose stromal vascular fraction cell therapy for multiple sclerosis. *J Transl Med.* 2009;7:29.
59. Gao S, Guo X, Zhao S, et al. Differentiation of human adipose-derived stem cells into neuron/motoneuron-like cells for cell replacement therapy of spinal cord injury. *Cell Death Dis.* 2019;10(8):597
60. Chi K, Fu RH, Huang YC, et al. Adipose-derived Stem Cells Stimulated with n-Butylideneophthalide Exhibit Therapeutic Effects in a Mouse Model of Parkinson's Disease. *Cell Transplant.* 2018;27(3):456-470.
61. Kim KS, Lee HJ, An J, et al. Transplantation of human adipose tissue-derived stem cells delays clinical onset and prolongs life span in ALS mouse model. *Cell Transplant.* 2014;23(12):1585-97.
62. Ma T, Gong K, Ao Q, et al. Intracerebral transplantation of adipose-derived mesenchymal stem cells alternatively activates microglia and ameliorates neuropathological deficits in Alzheimer's disease mice. *Cell Transplant.* 2013;22(1):113-26.
63. Kim S, Chang KA, Kim Ja, et al. The preventive and therapeutic effects of intravenous human adipose-derived stem cells in Alzheimer's disease mice. *PLoS One.* 2012;7(9):e45757.