Bölüm 4

KRONİK AĞRIDA MEZENKİMAL KÖK HÜCRE TEDAVİLERİ

Savaş ÇÖMLEK[1]

Rejeneratif tıp, hastalıkların tedavisinde vücudun kendi kendine özgü iyileştirici yöntem ve araçlarını geliştirerek kullanmayı hedefleyen bir uzmanlık alanıdır. Bu tedavinin amacı, otolog veya allojenik biyolojik maddeler kullanarak hasarlı dokuyu iyileştirmek veya eski haline getirmektir. Vücudun içsel onarım mekanizmasını uyarmak ya da bu mekanizma yetersiz kaldığında homolog veya otolog biyolojiklerle desteklemek rejeneratif tıbbın temelidir. Rejeneratif tıpta hücresel göç, replikasyon ve modellemeyi geliştirmek için biyomedikal, biyokimyasal ve biyomekanik teknolojiler kullanılmaktadır. Biyomedikal yaklaşımlar, mezenkimal stromal / kök hücrelerin (tıbbi sinyal hücreleri) veya progenitör hücrelerin tek başına veya biyolojik aktif moleküller ile birlikte immünomodülasyon sağlamak amacıyla uygulanmasını içerir. Aynı zamanda doku mühendisliği şemsiyesinin altına giren in vitro geliştirilen organ ve dokuların nakli de bu yaklaşımın içindedir (1-3).

Aslında kök hücreler, 1960'lardan bu yana lösemiyi tedavi etmek için kemik iliği nakli şeklinde klinikte kullanılmaktadır. Hematolojik hastalıkların yanı sıra yanık tedavisi, kemik grefti ve kornea nakli, kök hücre tedavisinin mevcut kullanımlarını örneklemektedir. Kök hücrelerin kullanılması, kemik ve kıkırdak defektleri, osteoartrit, tendon ve ligament yaralanmaları ve hatta sinir hasarı gibi ağrılı durumların tedavisi için de çözümler sunmaktadır (4,5). Bazı klinikler omurganın dejeneratif disklerine kök hücreler enjekte ederek başarılı sonuçlar almışlardır. Kesin bir sonuç için henüz çok erken olmasına rağmen, kök hücreler yalnızca kronik ağrı semptomlarını kontrol etmekle kalmaz, aynı zamanda hastalığın seyrini de değiştirebilirler. Bu derlemedeki hedefimiz ağrı tedavi alanında çalışan uzmanlara hücre bazlı terapiler konusundaki literatürün mevcut durumu hakkında genel bir bakış sağlamaktır.

Omurganın ve diğer kas-iskelet bozukluklarının rejeneratif tedavisinde kullanılan çeşitli biyolojik maddeler olsa da, Plazma Rich Platelet (PRP) ve Mezenkimal Kök Hücreler (MCS) rejeneratif ilaç tedavisinin güncel dayanak noktalarıdır.

[1] Dr, Gayrettepe Florence Nightingale Hastanesi, savatc@gmail.com

KAYNAKÇA

1. Manchikanti L, Navani A. Evolution of regenerative medicine in managing chronic pain. In: Manchikanti L, Navani A, Atluri S (eds). Essentials of Regenerative Medicine in Interventional Pain Management. ASIPP Publishing, Paducah, KY 2019, IN PRESS.
2. Lana JF, Purita J, Silva Rava CA, Nich- olls MA, Parada CA, Forti AP, Ventura Vierira IF, Madureira Junior JL, Fortis Gusmão PD, de Camargo LS, Caliari- Oliveira C. Bone marrow concentrate. In: Manchikanti L, Navani A, Atluri S (eds). Essentials of Regenerative Medi- cine in Interventional Pain Management. ASIPP Publishing, Paducah, KY 2019, IN PRESS.
3. Muneoka K, Allan CH, Yang X, Lee J; Han M. Mammalian regeneration and regenerative medicine. Birth Defects Res C Embryo Today 2008; 84:265-280.
4. Manchikanti L, Abdi S, Atluri S, et all.An up- date of comprehensive evidence-based guidelines for interventional techniques of chronic spinal pain: Part II: Guidance and recommendations. Pain Physician 2013; 16:S49-S283.
5. Manchikanti L, Kaye AM, Knezevic NN, et all. Responsible, safe, and effective pre-scription of opioids for chronic non-cancer pain: American Society of Interventional Pain Physicians (ASIPP) guidelines. Pain Physician 2017: 20:2S:S3-S92.
6. Caplan AI. Adult mesenchymal stem cells for tissue engineering versus re- generative medicine. J Cell Physiol 2007; 213:341-347.
7. Caplan AI. Cell delivery and tissue re- generation. J Control Release 1989; 11:157-165.
8. Caplan AI. Mesenchymal stem cells. J Orthop Res 1991; 9:641-650.
9. Caplan AI. Review: Mesenchymal stem cells: Cell-based reconstructive therapy in orthopedics. Tissue Eng 2005; 11:1198–1211.
10. Caplan AI. Mesenchymal stem cells: Time to change the name! Stem Cells Transl Med 2017; 6:1445-1451.
11. Kobolak J, Dinnyes A, Memic A, et al. Mesenchymal stem cells: Identification, phenotypic characterization, biological properties and potential for regenerative medicine through biomaterial micro-engineering of their niche. Methods 2016; 99:62-68.
12. Sclafani JA, Constantin A, Ho PS, Aku- thota V, Chan L. Descriptive analysis of spinal neuroaxial injections, surgical in- terventions, and physical therapy utiliza- tion for degenerative lumbar spondylo- listhesis within Medicare beneficiaries from 2000 to 2011. Spine (Phila Pa 1976) 2017; 42:240-246.
13. Rigotti G, Marchi A, Sbarbati A. Adipose- derived mesenchymal stem cells: Past, present, and future. Aesthetic Plast Surg 2009; 33:271-273.
14. Ghosh P., Moore R., Vernon-Roberts B., et al. Immunoselected STRO-3+ mesenchymal precursor cells and restoration of the extracellular matrix of degenerate intervertebral discs: laboratory investigation. Journal of Neurosurgery: Spine. 2012;16(5):479–488. doi: 10.3171/2012.1.spine11852.
15. Sakai D., Mochida J., Iwashina T., et al. Regenerative effects of transplanting mesenchymal stem cells embedded in atelocollagen to the degenerated intervertebral disc. Biomaterials. 2006;27(3):335–345. doi: 10.1016/j.biomaterials.2005.06.038.
16. Sakai D., Mochida J., Iwashina T., et al. Differentiation of mesenchymal stem cells transplanted to a rabbit degenerative disc model: potential and limitations for stem cell therapy in disc regeneration. Spine. 2005;30(21):2379–2387. doi: 10.1097/01.brs.0000184365.28481.e3.
17. Sobajima S., Vadala G., Shimer A., et al.Feasibility of a stem cell therapy for intervertebral disc degeneration. Spine Journal. 2008;8(6):888–896. doi: 10.1016/j.spinee.2007.09.011.
18. Hiyama A., Mochida J., Iwashina T., et al. Transplantation of mesenchymal stem cells in a canine disc degeneration model. Journal of Orthopaedic Research. 2008;26(5):589–600. doi: 10.1002/jor.20584.
19. Henriksson H. B., Svanvik T., Jonsson M., et al. Transplantation of human mesenchymal stems cells into intervertebral discs in a xenogeneic porcine model. Spine. 2009;34(2):141–148. doi: 10.1097/BRS.0b013e31818f8c20.

20. Rajpurohit R., Risbud M. V., Ducheyne P., Vresilovic E. J., Shapiro I. M. Phenotypic characteristics of the nucleus pulposus: expression of hypoxia inducing factor-1, glucose transporter-1 and MMP-2. Cell and Tissue Research. 2002;308(3):401–407. doi: 10.1007/s00441-002-0563-6.
21. Crevensten G., Walsh A. J. L., Ananthakrishnan D., et al. Intervertebral disc cell therapy for regeneration: mesenchymal stem cell implantation in rat intervertebral discs. Annals of Biomedical Engineering. 2004;32(3):430–434. doi: 10.1023/b:abme.0000017545.84833.7c.
22. Minogue B. M., Richardson S. M., Zeef L. et al. Characterization of the human nucleus pulposus cell phenotype and evaluation of novel marker gene expression to define adult stem cell differentiation. Arthritis & Rheumatism. 2010;62(12):3695–3705. doi: 10.1002/art.27710.
23. Longo U. G., Papapietro N., Petrillo S., et al. Mesenchymal stem cell for prevention and management of intervertebral disc degeneration. Stem Cells International. 2012;2012:7. doi: 10.1155/2012/921053.921053
24. Gilbert H. T. J., Hoyland J. A., Richardson S. M. Stem cell regeneration of degenerated intervertebral discs: current status (Update) Current Pain and Headache Reports. 2013;17, article 377doi: 10.1007/s11916-013-0377-0.
25. Gimble J. M., Katz A. J., Bunnell B. A. Adipose-derived stem cells for regenerative medicine. Circulation Research. 2007;100(9):1249–1260. doi: 10.1161/01.res.0000265074.83288.09.
26. Lu L.-L., Liu Y.-J., Yang S.-G., 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.
27. Chen K., Wang D., Du W. T., et al. Human umbilical cord mesenchymal stem cells hUC-MSCs exert immunosuppressive activities through a PGE2-dependent mechanism. Clinical Immunology. 2010;135(3):448–458. doi: 10.1016/j.clim.2010.01.015.
28. Centeno C. J. Clinical challenges and opportunities of mesenchymal stem cells in musculoskeletal medicine. PM&R. 2014;6(1):70–77. doi: 10.1016/j.pmrj.2013.08.612.
29. Koleva G. Stem Cells, FDA, and the Edge of Science: Three Expert Viewpoints. Pharma & Healthcare; 2012. http://www.forbes.com/sites/gerganakoleva/2012/02/19/stem-cells-fda-and-the-edge-of-science-three-expert-viewpoints/
30. Tanaka M., Sakai D., Hiyama A., et al. Effect of cryopreservation on canine and human activated nucleus pulposus cells: a feasibility study for cell therapy of the intervertebral disc. BioRes Open Access. 2013;2(4):273–282. doi: 10.1089/biores.2013.0023.
31. Liu H., Kemeny D. M., Heng B. C., et al.The immunogenicity and immunomodulatory function of osteogenic cells differentiated from mesenchymal stem cells. Journal of Immunology. 2006;176(5):2864–2871. doi: 10.4049/jimmunol.176.5.2864.
32. Risbud MV, Albert TJ, Guttapalli A, et al. Differentiation of mesenchymal stem cells towards a nucleus-pulposus like phenotype in vitro: Implications for cell-based transplantation therapy. Spine 2004; 29:1508-1514.
33. Vickers ER, Karsten E, Flood J, Lilisch- kis R. A preliminary report on stem cell therapy for neuropathic pain in humans. J Pain Res 2014; 7:255-263.
34. Kirkaldy-Willis WH, Wedge JH, Yong- Hing K, er al. Lumbar spinal nerve lateral entrapment. Clin Orthop Relat Res 1982; 169:171-178.
35. Depalma M. Biologic treatments for discogenic low back pain. SpineLine 2012; 13:19-23.
36. Wei A, Shen B, Williams L, Diwan A. Mesenchymal stem cells: Potential ap- plication in intervertebral disc regeneration. Transl Pediatr 2014; 3:71-90.
37. Comella K, Silbert R, Parlo M. Effects of the intradiscal implantation of stromal vascular fraction plus platelet rich plas- ma in patients with degenerative disc disease. J Transl Med 2017; 15:12.
38. Buchanan RM, Blashki D, Murphy MB. Stem cell therapy for regenerative medi- cine. Chem Eng Prog 2014; 110:55-58.
39. Bogduk N. Clinical and Radiological Anatomy of the Lumbar Spine. 5th ed. El- sevier Churchill Livingstone, 2012.

40. Iatridis JC, Nicoll SB, Michalek AJ, Wal- ter BA, Gupta MS. Role of biomechan- ics in intervertebral disc degeneration and regenerative therapies: what needs repairing in the disc and what are prom- ising biomaterials for its repair? Spine J 2013; 13:243-262.
41. Bogduk N, Aprill C, Derby R. Lumbar discogenic pain: State-of-the-art review. Pain Med 2013; 14:813-836.
42. Manchikanti L, Albers SL, Hirsh JA, Bo- swell, MV. Lumbar Disk Herniation. In: Kaye AD, ed. Scientific American Pain Management. Hamilton: Decker; Sep- tember 2017. DOI: 10.2310/7900.15047. www.DeckerIP.com
43. Zeckser J, Wolff M, Tucker J, Goodwin J. Multipotent mesenchymal stem cell treatment for discogenic low back pain and disc degeneration. Stem Cells Int 2016; 2016:3908389.
44. Fairbank JC, Pynsent PB. The Oswestry Disability Index. Spine (Phila Pa 1976) 2000; 25:2940-2952
45. Chen WH, Lo WC, Lee JJ, et al. Tissue-engineered inter- vertebral disc and chondrogenesis us- ing human nucleus pulposus regulated through TGF-beta1 in platelet-rich plas- ma. J Cell Physiol 2006; 209:744-754.
46. Gullung GB, Woodall JW, Tucci MA, James J, Black DA, McGuire RA. Platelet- rich plasma effects on degenerative disc disease: analysis of histology and imag- ing in an animal model. Evid Based Spine Care J 2011; 2:13-18.
47. Obata S, Akeda K, Imanishi T, et al. Effect of autologous platelet-rich plasma-releasate on intervertebral disc degeneration in the rab- bit anular puncture model: a preclinical study. Arthritis Res Ther 2012; 14:R241.
48. Hohaus C., Ganey T. M., Minkus Y., Meisel H. J. Cell transplantation in lumbar spine disc degeneration disease. European Spine Journal. 2008;17(4):S492–S503. doi: 10.1007/s00586-008-0750-6.
49. Yoshida R, Cheng M, Murray MM. Increasing platelet concentration in platelet-rich plasma inhibits anterior cruciate ligament cell function in three- dimensional culture. J Orthop Res 2014; 32:291-295.
50. Wasterlain AS, Braun HJ, Harris AH, Kim HJ, Dragoo JL. The systemic effects of platelet-rich plasma injection. Am J Sports Med 2013; 41:186-193.
51. Manchikanti L, Navani A. Lumbar facet joints and regenerative medicine. In: Manchikanti L, Navani A, Atluri S (eds). Essentials of Regenerative Medicine in In- terventional Pain Management. ASIPP Publishing, Paducah, KY 2018, pp
52. Kristjánsson B, Limthongkul W, Ying- sakmongkol W, Thantiworasit P, Ji- rathanathornnukul N, Honsawek S. Isolation and characterization of hu- man mesenchymal stem cells from facet joints and interspinous ligaments. Spine (Phila Pa 1976) 2016; 41:E1-E7.
53. Richardson SM, Kalamegam G, Push- paraj PN, et al. Mesenchymal stem cells in regenerative medicine: Fo- cus on articular cartilage and interver- tebral disc regeneration. Methods 2016; 99:69-80.
54. Cabaret J, Manchikanti L, Calodney AK. Regenerative medicine for sacro- iliac joint dysfunction. In: Manchikanti L, Navani A, Atluri S (eds). Essentials of Regenerative Medicine in Interventional Pain Management. ASIPP Publishing,
55. Graziani F, Ivanovski S, Cei S, et al. The in vitro ef- fect of different PRP concentrations on osteoblasts and fibroblasts. Clin Oral Im- plants Res 2006; 17:212-219.
56. Angele P, Kujat R, Koch M, Zellner J. Role of mesenchymal stem cells in meniscal repair. Journal of Experimental Orthopaedics 2014; 1:12.
57. Nepple JJ, Dunn WR, Wright RW. Meniscal repair outcomes at greater than five years: A systematic literature review and meta-analysis. J Bone Joint Surg Am 2012; 94:2222-2227.
58. Iijima H., Isho T., Kuroki H., Takahashi M., Aoyama T. Effectiveness of mesenchymal stem cells for treating patients with knee osteoarthritis: A meta-analysis toward the establishment of effective regenerative rehabilitation. NPJ Regen. Med. 2018;3:15. doi: 10.1038/s41536-018-0041-8.
59. Peeters CM, Lejs MJ, Reijman M, van Osch GJ, Bos PK. Safety of intra-articular cell therapy with culture-expanded stem cells in humans: A systematic literature review. Osteoarthritis Cartilage 2013; 21:1465-1473.

60. Jo CH, Lee YG, Shin WH, Kim H, Chai JW, Jeong EC, Kim JE, Shim H, Shin JS, Shin IS, Ra JC, Oh S, Yoon KS. Intra-ar- ticular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: A proof-of-concept clinical trial. Stem Cells 2014; 32:1254-1266.
61. Emadedin M, Aghdami N, Taghiyar L, et al. Intra- articular injection of autologous mesenchymal stem cells in six patients with knee osteoarthritis. Arch Iran Med 2012; 15:422-428.
62. Yousefifard M, Nasirinezhad F, Shardi Manaheji H, et al. Human bone marrow- derived and umbilical cord-derived mesenchymal stem cells for alleviating neuropathic pain in a spinal cord inju- ry model. Stem Cell Research & Therapy 2016; 7:36.
63. Vickers ER, Karsten E, Flood J, Lilisch- kis R. A preliminary report on stem cell therapy for neuropathic pain in humans. J Pain Res 2014; 7:255-26
64. Venturi M, Boccasanta P, Lombardi B, Brambilla M, Contessini Avesani E, Ver- gani C. Pudendal neuralgia: A new op- tion for treatment? Preliminary results on feasibility and efficacy. Pain Med 2015; 16:1475-1481.
65. Marks PW, Witten CM, Califf CM. Clari- fying stem-cell therapy's benefits and risks. N Engl J Med 2016; 376:1007-1009.
66. Knoepfler PS. From bench to FDA to bedside: US regulatory trends for new stem cell therapies. Adv Drug Deliv Rev 2015; 82-83:192-196.
67. FDA News Release. FDA acts to remove unproven, potentially harmful treat- ment used in 'stem cell' centers target- ing vulnerable patients. Vaccinia Virus Vaccine (Live) seized after being used inappropriately in vulnerable cancer pa- tients. August 28, 2017. www.fda.gov/NewsEvents/Newsroom/ PressAnnouncements/ucm573427.htm
68. Turner LG. Federal regulatory oversight of US clinics marketing adipose-derived autologous stem cell interventions: Insights from 3 new FDA draft guid- ance documents. Mayo Clin Proc 2015; 90:567-571.
69. Turner L. US stem cell clinics, patient safety, and the FDA. Trends Mol Med 2015; 21:271-273.
70. Charo A, Sipp D. Rejuvenating regener- ative medicine regulation. N Engl J Med 2018; 378:504-505.
71. World Health Organization. Transplan- tation: Transplantation of human cells, tissues, and organs. www.who.int/ transplantation/en/
72. Marks P, Gottlieb S. Balancing safety and innovation for cell-based regen- erative medicine. N Engl J Med 2018 378:954-959.
73. Regulatory Considerations for Human Cell, Tissues, and Cellular and Tissue- Based Products: Minimal Manipulation and Homologous Use. Guidance for In- dustry and Food and Drug Administra- tion Staff, November 2017. www.fda.gov/downloads/Biologics- BloodVaccines/GuidanceCompliance- RegulatoryInformation/Guidances/Cel- lularandGeneTherapy/UCM585403.pdf
74. Berman M, Lander E. Regulatory is- sues with human cells: An alternate view. In: Manchikanti L, Navani A, Atluri S (eds). Essentials of Regenerative Medi- cine in Interventional Pain Management. ASIPP Publishing, Paducah, KY 2019, IN PRES