

## Bölüm 10

# KIKIRDAK DOKU MÜHENDİSLİĞİ VE YENİ TEKNİKLER

Altuğ YÜCEKUL<sup>1</sup>

### GİRİŞ

Eklem kıkırdağının rejenerasyonu, kıkırdak biçimlenmesini başlatan faktörlerin, kıkırdağın olgunlaşmasında ve iyileşmesindeki bilinmeyenler nedeniyle, tam olarak aydınlatılamamıştır. Avasküler yapısı, seyrek hücre nüfusu içermesi, kondrositlerin düşük mitotik aktivitesi (1) gibi sebeplerden, yaralanma, hastalık veya aşınma nedeniyle hasar gören eklem kıkırdağının çok kısıtlı bir iyileşme potansiyeli bulunmaktadır. Tedavi edilmemiş bir veya birden fazla kıkırdak hasarı varlığında, lezyonların derin laserasyonlar yarattığı ve kendiliğinden iyileşme potansiyelinin olmadığı gösterilmiştir (2). Bu nedenlerle kıkırdak rejenerasyonu, günümüz tıbbında en zorlayıcı konulardan birini oluşturmaktadır.

Sağlıklı eklem kıkırdağı; su, kıkırdağın kompresif kuvvetini sağlayan proteoglikanlar ve tensil kuvvetini sağlayan tip 2 kollajenleri içeren hyalin kıkırdağı üretebilen, kolumnar büyüme modeline sahip kondrositler ile karakterizedir. Tam kat olmıyan kıkırdak defektlerinin derinlikleri, subkondral kemiğe ulaşamadığında, inflamatuvar cevap oluşturmamakta, iyileşme görülmemekte ve vaskülerite de olmadığı için defekt zamanla büyümektedir. Tam kat eklem defektlerinin iyileşme ve restorasyonunu gösteren çalışmalarda ise, iyileşme dokusunun, makromoleküler ve biyomekanik karakterlerinin eksik olduğu, sürecin ilk olarak fibrin tıkaç ile başladığı (3), andiferansiye mezenkimal kök hücrelerin migrasyonu ve diferansiasyonu için yüzeyin yüklerden korunması gerektiği (4) ve bütün süreçlerin, eklem yüzeyinde, tip 2 yerine tip 1 kollajenden zengin fibrokartilaj doku oluşumuyla neticelendiği gösterilmiştir (5). Günümüzde uygulanan tedavi ile hedeflenen ise eklem kıkırdağının tam yük taşıma kapasitesine geri döndürebilecek, defektin çevresindeki kıkırdak dokular ile birleşecek, tip 2 kollajen ve çeşitli pro-

<sup>1</sup> Uzman Doktor, Acıbadem Maslak Hastanesi Omurga Sağlığı ayucekul@gmail.com

gelişim göstermektedir. Osteokondral oto-allogreft transferinden, otolog ve allo kondrosit implantasyonuna genişleyen yelpazede sitokin, kök hücre ve doku mühendisliği yapıları kullanılarak gerçekleştirilen rejeneratif yaklaşımların endikasyonları ve birbirine üstünlüklerini gösteren yönleri bilinmemektedir (58). Kıkırdak doku mühendisliği konusunda daha ileri ve kapsamlı çalışmalara ihtiyaç bulunmaktadır. Literatürdeki çalışmaların çoğu prelinik araştırmalar olup, kıkırdağın biyolojik tamirinin klinik olarak uygulanabilir hale gelebilmesi için, en iyi hücre kaynağı, en iyi toplama yöntemi, en etkin doz, uygun endikasyonlar gibi soruların randomize kontrollü çalışmalar ile aydınlatılması gerekmektedir.

## **KAYNAKLAR**

1. Ushida T, Furukawa K, Toita K, ve ark. Three-dimensional seeding of chondrocytes encapsulated in collagen gel into PLLA scaffolds. *Cell Transplant*. 2002;11(5):489-94.
2. Mankin HJ. The response of articular cartilage to mechanical injury. *J Bone Joint Surg Am*. 1982;64(3):460-6.
3. Buckwalter JA, Mankin HJ. Articular cartilage: degeneration and osteoarthritis, repair, regeneration, and transplantation. *Instr Course Lect*. 1998;47:487-504.
4. Shapiro F, Koide S, Glimcher MJ. Cell origin and differentiation in the repair of full-thickness defects of articular cartilage. *J Bone Joint Surg Am*. 1993;75(4):532-53.
5. Nehrer S, Spector M, Minas T. Histologic analysis of tissue after failed cartilage repair procedures. *Clin Orthop Relat Res*. 1999(365):149-62.
6. Cole BJ, Pascual-Garrido C, Grumet RC. Surgical management of articular cartilage defects in the knee. *J Bone Joint Surg Am*. 2009;91(7):1778-90.
7. Breinan HA, Martin SD, Hsu HP, ve ark. Healing of canine articular cartilage defects treated with microfracture, a type-II collagen matrix, or cultured autologous chondrocytes. *J Orthop Res*. 2000;18(5):781-9.
8. Gobbi A, Karnatzikos G, Sankineani SR. One-step surgery with multipotent stem cells for the treatment of large full-thickness chondral defects of the knee. *Am J Sports Med*. 2014;42(3):648-57.
9. Brucker PU, Braun S, Imhoff AB. [Mega-OATS technique--autologous osteochondral transplantation as a salvage procedure for large osteochondral defects of the femoral condyle]. *Oper Orthop Traumatol*. 2008;20(3):188-98.
10. Yamashita F, Sakakida K, Suzu F, ve ark. The transplantation of an autogeneic osteochondral fragment for osteochondritis dissecans of the knee. *Clin Orthop Relat Res*. 1985(201):43-50.
11. Hangody L, Fules P. Autologous osteochondral mosaicplasty for the treatment of full-thickness defects of weight-bearing joints: ten years of experimental and clinical experience. *J Bone Joint Surg Am*. 2003;85-A Suppl 2:25-32.
12. Baltzer AW, Arnold JP. Bone-cartilage transplantation from the ipsilateral knee for chondral lesions of the talus. *Arthroscopy*. 2005;21(2):159-66.
13. Lane JG, Massie JB, Ball ST, ve ark. Follow-up of osteochondral plug transfers in a goat model: a 6-month study. *Am J Sports Med*. 2004;32(6):1440-50.
14. Paul J, Sagstetter A, Kriner M, ve ark. Donor-site morbidity after osteochondral autologous transplantation for lesions of the talus. *J Bone Joint Surg Am*. 2009;91(7):1683-8.
15. Kreuz PC, Steinwachs M, Erggelet C, ve ark. Mosaicplasty with autogenous talar autograft for osteochondral lesions of the talus after failed primary arthroscopic management: a prospective study with a 4-year follow-up. *Am J Sports Med*. 2006;34(1):55-63.
16. Marcacci M, Kon E, Delcogliano M, ve ark. Arthroscopic autologous osteochondral grafting for cartilage defects of the knee: prospective study results at a minimum 7-year follow-up. *Am*

- J Sports Med. 2007;35(12):2014-21.
17. Aubin PP, Cheah HK, Davis AM, ve ark. Long-term followup of fresh femoral osteochondral allografts for posttraumatic knee defects. *Clin Orthop Relat Res.* 2001(391 Suppl):S318-27.
  18. LaPrade RF, Botker J, Herzog M, ve ark. Refrigerated osteoarticular allografts to treat articular cartilage defects of the femoral condyles. A prospective outcomes study. *J Bone Joint Surg Am.* 2009;91(4):805-11.
  19. Bedi A, Feeley BT, Williams RJ, 3rd. Management of articular cartilage defects of the knee. *J Bone Joint Surg Am.* 2010;92(4):994-1009.
  20. Filardo G, Kon E, Di Martino A, ve ark. Second-generation arthroscopic autologous chondrocyte implantation for the treatment of degenerative cartilage lesions. *Knee Surg Sports Traumatol Arthrosc.* 2012;20(9):1704-13.
  21. Filardo G, Kon E, Roffi A, ve ark. Scaffold-based repair for cartilage healing: a systematic review and technical note. *Arthroscopy.* 2013;29(1):174-86.
  22. Brittberg M, Lindahl A, Nilsson A, ve ark. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. *N Engl J Med.* 1994;331(14):889-95.
  23. von der Mark K, Gauss V, von der Mark H, ve ark. Relationship between cell shape and type of collagen synthesised as chondrocytes lose their cartilage phenotype in culture. *Nature.* 1977;267(5611):531-2.
  24. Benya PD, Shaffer JD. Dedifferentiated chondrocytes reexpress the differentiated collagen phenotype when cultured in agarose gels. *Cell.* 1982;30(1):215-24.
  25. Kon E, Verdonk P, Condello V, ve ark. Matrix-assisted autologous chondrocyte transplantation for the repair of cartilage defects of the knee: systematic clinical data review and study quality analysis. *Am J Sports Med.* 2009;37 Suppl 1:156S-66S.
  26. Grigolo B, Lisignoli G, Piacentini A, ve ark. Evidence for redifferentiation of human chondrocytes grown on a hyaluronan-based biomaterial (HYAff 11): molecular, immunohistochemical and ultrastructural analysis. *Biomaterials.* 2002;23(4):1187-95.
  27. Marcacci M, Zaffagnini S, Kon E, ve ark. Arthroscopic autologous chondrocyte transplantation: technical note. *Knee Surg Sports Traumatol Arthrosc.* 2002;10(3):154-9.
  28. Erggelet C, Sittlinger M, Lahm A. The arthroscopic implantation of autologous chondrocytes for the treatment of full-thickness cartilage defects of the knee joint. *Arthroscopy.* 2003;19(1):108-10.
  29. Kreuz PC, Muller S, Ossendorf C, ve ark. Treatment of focal degenerative cartilage defects with polymer-based autologous chondrocyte grafts: four-year clinical results. *Arthritis Res Ther.* 2009;11(2):R33.
  30. Gomoll AH, Filardo G, de Girolamo L, ve ark. Surgical treatment for early osteoarthritis. Part I: cartilage repair procedures. *Knee Surg Sports Traumatol Arthrosc.* 2012;20(3):450-66.
  31. Schmidt MB, Chen EH, Lynch SE. A review of the effects of insulin-like growth factor and platelet derived growth factor on in vivo cartilage healing and repair. *Osteoarthritis Cartilage.* 2006;14(5):403-12.
  32. Pujol JP, Chadjichristos C, Legendre F, ve ark. Interleukin-1 and transforming growth factor-beta 1 as crucial factors in osteoarthritic cartilage metabolism. *Connect Tissue Res.* 2008;49(3):293-7.
  33. Brehm W, Aklin B, Yamashita T, ve ark. Repair of superficial osteochondral defects with an autologous scaffold-free cartilage construct in a caprine model: implantation method and short-term results. *Osteoarthritis Cartilage.* 2006;14(12):1214-26.
  34. Munirah S, Samsudin OC, Chen HC, ve ark. Articular cartilage restoration in load-bearing osteochondral defects by implantation of autologous chondrocyte-fibrin constructs: an experimental study in sheep. *J Bone Joint Surg Br.* 2007;89(8):1099-109.
  35. Yucekul A, Ozdil D, Kutlu NH, ve ark. Tri-layered composite plug for the repair of osteochondral defects: in vivo study in sheep. *J Tissue Eng.* 2017;8:2041731417697500.
  36. Jelic M, Pecina M, Haspl M, ve ark. Regeneration of articular cartilage chondral defects by osteogenic protein-1 (bone morphogenetic protein-7) in sheep. *Growth Factors.* 2001;19(2):101-13.

37. Mont MA, Ragland PS, Biggins B, ve ark. Use of bone morphogenetic proteins for musculoskeletal applications. An overview. *J Bone Joint Surg Am.* 2004;86-A Suppl 2:41-55.
38. Mironov V, Visconti RP, Kasyanov V, ve ark. Organ printing: tissue spheroids as building blocks. *Biomaterials.* 2009;30(12):2164-74.
39. Waldman SD, Grynepas MD, Pilliar RM, ve ark. Characterization of cartilagenous tissue formed on calcium polyphosphate substrates in vitro. *J Biomed Mater Res.* 2002;62(3):323-30.
40. Furukawa KS, Imura K, Tateishi T, ve ark. Scaffold-free cartilage by rotational culture for tissue engineering. *J Biotechnol.* 2008;133(1):134-45.
41. Stoddart MJ, Ettinger L, Hauselmann HJ. Generation of a scaffold free cartilage-like implant from a small amount of starting material. *J Cell Mol Med.* 2006;10(2):480-92.
42. Kelm JM, Djonov V, Ittner LM, ve ark. Design of custom-shaped vascularized tissues using microtissue spheroids as minimal building units. *Tissue Eng.* 2006;12(8):2151-60.
43. Jakob M, Demarteau O, Schafer D, ve ark. Specific growth factors during the expansion and redifferentiation of adult human articular chondrocytes enhance chondrogenesis and cartilaginous tissue formation in vitro. *J Cell Biochem.* 2001;81(2):368-77.
44. Domm C, Schunke M, Christesen K, ve ark. Redifferentiation of dedifferentiated bovine articular chondrocytes in alginate culture under low oxygen tension. *Osteoarthritis Cartilage.* 2002;10(1):13-22.
45. Lee CR, Grodzinsky AJ, Spector M. Biosynthetic response of passaged chondrocytes in a type II collagen scaffold to mechanical compression. *J Biomed Mater Res A.* 2003;64(3):560-9.
46. Lodi D, Iannitti T, Palmieri B. Stem cells in clinical practice: applications and warnings. *J Exp Clin Cancer Res.* 2011;30:9.
47. Filardo G, Madry H, Jelic M, ve ark. Mesenchymal stem cells for the treatment of cartilage lesions: from preclinical findings to clinical application in orthopaedics. *Knee Surg Sports Traumatol Arthrosc.* 2013;21(8):1717-29.
48. Cucchiari M, Madry H. Genetic modification of mesenchymal stem cells for cartilage repair. *Biomed Mater Eng.* 2010;20(3):135-43.
49. Venkatesan JK, Ekici M, Madry H, ve ark. SOX9 gene transfer via safe, stable, replication-defective recombinant adeno-associated virus vectors as a novel, powerful tool to enhance the chondrogenic potential of human mesenchymal stem cells. *Stem Cell Res Ther.* 2012;3(3):22.
50. Carney EF. Regenerative medicine: Adipose stem cells fail to boost cartilage repair in rats. *Nat Rev Rheumatol.* 2012;8(10):563.
51. Sakaguchi Y, Sekiya I, Yagishita K, ve ark. Comparison of human stem cells derived from various mesenchymal tissues: superiority of synovium as a cell source. *Arthritis Rheum.* 2005;52(8):2521-9.
52. De Bari C, Dell'Accio F, Tylzanowski P, ve ark. Multipotent mesenchymal stem cells from adult human synovial membrane. *Arthritis Rheum.* 2001;44(8):1928-42.
53. Jones E. Synovial mesenchymal stem cells in vivo: Potential key players for joint regeneration. *World Journal of Rheumatology.* 2011;1:4.
54. Ando W, Tateishi K, Hart DA, ve ark. Cartilage repair using an in vitro generated scaffold-free tissue-engineered construct derived from porcine synovial mesenchymal stem cells. *Biomaterials.* 2007;28(36):5462-70.
55. Ando W, Tateishi K, Katakai D, ve ark. In vitro generation of a scaffold-free tissue-engineered construct (TEC) derived from human synovial mesenchymal stem cells: biological and mechanical properties and further chondrogenic potential. *Tissue Eng Part A.* 2008;14(12):2041-9.
56. Katakai D, Imura M, Ando W, ve ark. Compressive properties of cartilage-like tissues repaired in vivo with scaffold-free, tissue engineered constructs. *Clin Biomech (Bristol, Avon).* 2009;24(1):110-6.
57. Nestic D, Whiteside R, Brittberg M, ve ark. Cartilage tissue engineering for degenerative joint disease. *Adv Drug Deliv Rev.* 2006;58(2):300-22.
58. Marcacci M, Filardo G, Kon E. Treatment of cartilage lesions: what works and why? *Injury.* 2013;44 Suppl 1:S11-5.