BÖLÜM 1

REJENERATİF ENDODONTİK TEDAVİNİN TEMEL BİLEŞENLERİ: KÖK HÜCRELER, BÜYÜME FAKTÖRLERİ VE İSKELELER

Emine ŞİMŞEK[1]

GİRİŞ

Rejeneratif endodontik tedavi (RET), geleneksel kök kanal tedavilerine alternatif olarak geliştirilen ve dişin doğal pulpa-dentin kompleksini yeniden oluşturmayı hedefleyen biyolojik temelli bir yaklaşım olarak bilinmektedir (1). Diş pulpası, dişin canlılığını sürdürmesinde kritik rol oynayan, beslenme, duyu iletimi ve savunma gibi birçok işlevi üstlenen yumuşak bir dokudur (2,3). Pulpa dokusunun enfekte veya nekrotik hale gelmesi durumunda uygulanan geleneksel tedaviler enfeksiyonu ortadan kaldırsa da, dokunun kaybı nedeniyle dişin doğal işlevleri geri kazanılamamaktadır.

RET, doku mühendisliği prensiplerine dayanarak, hasarlı veya kaybolmuş pulpa dokusunun yerine biyolojik olarak aktif yeni bir doku oluşturmayı amaçlamaktadır (4,5). Bu süreç; kök hücreler, büyüme faktörleri ve biyolojik iskele sistemleri gibi temel unsurların bir araya getirilmesiyle gerçekleştirilir. Özellikle genç, kök gelişimi tamamlanmamış dişlerde uygulanan rejeneratif tedaviler, kök gelişiminin devam etmesini sağlayarak dişin uzun dönem prognozunu iyileştirmektedir (6,7).

Günümüzde en yaygın RET yöntemi revaskülarizasyondur ve kök kanalına kan pıhtısı, trombosit bakımından zengin plazma (PRP) veya trombosit açısından zengin fibrin (PRF) yerleştirilerek kök hücrelerin kanal içine çekilmesi sağlanmaktadır. Ancak, revaskülarizasyonla gerçek pulpa dokusu oluşamayabileceği için, kök hücre nakli ve hücre çağırma gibi alternatif stratejiler geliştirilmektedir (5,6). Kök hücre naklinde, kök hücreler büyüme faktörleri ve iskelelerle kök ka-

---

[1] Dr. Öğr.Üyesi, Mersin Üniversitesi, Diş Hekimliği Fakültesi Endodonti AD., eminesimsek@mersin.edu.tr, ORCID iD: 0000-0001-9195-2012

DOI: 10.37609/akya.3813.c700

KAYNAKLAR

1. Murray PE, Garcia-Godoy F, Hargreaves KM. Regenerative endodontics: A review of current status and a call for action. *Journal of Endodontics*. 2007;33:377–390.
2. Nör JE. Tooth regeneration in operative dentistry. *Operative Dentistry*. 2006;31:633–642.
3. Fan Y, Zhou Y, Zhou X, et al. MicroRNA 224 regulates ion transporter expression in ameloblasts to coordinate enamel mineralization. *Molecular and Cellular Biology*. 2015;35:2875–2890.
4. Hashemi-Beni B, Khoroushi M, Foroughi MR, et al. Tissue engineering: Dentin—Pulp complex regeneration approaches (a review). *Tissue and Cell*. 2017;49:552–564.
5. Eramo S, Natali A, Pinna R, et al. Dental pulp regeneration via cell homing. *International Endodontic Journal*. 2018;51:405–419.
6. Xie Z, Shen Z, Zhan P, et al. Functional dental pulp regeneration: Basic research and clinical translation. *International Journal of Molecular Sciences*. 2021;22:8991.
7. Sui B, Chen C, Kou X, et al. Pulp stem cell-mediated functional pulp regeneration. *Journal of Dental Research*. 2019;98:27–35.
8. Hakim LK, Yazdanian M, Alam M, et al. Biocompatible and biomaterials application in drug delivery system in oral cavity. *Evidence-Based Complementary and Alternative Medicine*. 2021;2021:9011226.
9. Diogenes A. Trigeminal sensory neurons and pulp regeneration. *Journal of Endodontics*. 2020;46:S71–S80.
10. Botelho J, Cavacas MA, Machado V, et al. Dental stem cells: Recent progresses in tissue engineering and regenerative medicine. *Annals of Medicine*. 2017;49:644–651.
11. Lyu P, Li B, Li P, et al. Parathyroid hormone 1 receptor signaling in dental mesenchymal stem cells: Basic and clinical implications. *Frontiers in Cell and Developmental Biology*. 2021;9:654715.
12. Bi R, Lyu P, Song Y, et al. Function of dental follicle progenitor/stem cells and their potential in regenerative medicine: From mechanisms to applications. *Biomolecules*. 2021;11:997.
13. Soudi A, Yazdanian M, Ranjbar R, et al. Role and application of stem cells in dental regeneration: A comprehensive overview. *EXCLI Journal*. 2021;20:454–489.
14. Cui C, Bi R, Liu W, et al. Role of PTH1R signaling in Prx1(+) mesenchymal progenitors during eruption. *Journal of Dental Research*. 2020;99:1296–1305.
15. Gronthos S, Mankani M, Brahim J, et al. Postnatal human dental pulp stem cells (DPSCs) in vitro and in vivo. *Proceedings of the National Academy of Sciences of the United States of America*. 2000;97:13625–13630.
16. Wang LH, Gao SZ, Bai XL, et al. An up-to-date overview of dental tissue regeneration using dental origin mesenchymal stem cells: Challenges and road ahead. *Frontiers in Bioengineering and Biotechnology*. 2022;10:855396.
17. Gronthos S, Brahim J, Li W, et al. Stem cell properties of human dental pulp stem cells. *Journal of Dental Research*. 2002;81:531–535.
18. Nakamura S, Yamada Y, Katagiri W, et al. Stem cell proliferation pathways comparison between human exfoliated deciduous teeth and dental pulp stem cells by gene expression profile from promising dental pulp. *Journal of Endodontics*. 2009;35:1536–1542.
19. Martinez Saez D, Sasaki RT, Neves AD, et al. Stem cells from human exfoliated deciduous teeth: A growing literature. *Cells Tissues Organs*. 2016;202:269–280.
20. Miura M, Gronthos S, Zhao M, et al. SHED: Stem cells from human exfoliated deciduous teeth. *Proceedings of the National Academy of Sciences of the United States of America*. 2003;100:5807–5812.
21. Oubenyahya H. Stem cells from dental pulp of human exfoliated teeth: Current understanding and future challenges in dental tissue engineering. *Chinese Journal of Dental Research*. 2021;24:9–20.
22. Pereira LV, Bento RF, Cruz DB, et al. Stem cells from human exfoliated deciduous teeth (SHED) differentiate in vivo and promote facial nerve regeneration. *Cell Transplantation*. 2019;28:55–64.

23. Feng X, Xing J, Feng G, et al. Age-dependent impaired neurogenic differentiation capacity of dental stem cell is associated with Wnt/β-catenin signaling. *Cellular and Molecular Neurobiology*. 2013;33:1023–1031.
24. Seo BM, Miura M, Gronthos S, et al. Investigation of multipotent postnatal stem cells from human periodontal ligament. *The Lancet*. 2004;364:149–155.
25. Chen FM, Gao LN, Tian BM, et al. Treatment of periodontal intrabony defects using autologous periodontal ligament stem cells: A randomized clinical trial. *Stem Cell Research & Therapy*. 2016;7:33.
26. Tomokiyo A, Wada N, Maeda H. Periodontal ligament stem cells: Regenerative potency in periodontium. *Stem Cells and Development*. 2019;28:974–985.
27. Zhai Q, Dong Z, Wang W, et al. Dental stem cell and dental tissue regeneration. *Frontiers of Medicine*. 2019;13:152–159.
28. Janebodin K, Horst OV, Ieronimakis N, et al. Isolation and characterization of neural crest-derived stem cells from dental pulp of neonatal mice. *PLoS ONE*. 2011;6:e27526.
29. Smeda M, Galler KM, Woelflick M, et al. Molecular biological comparison of dental pulp- and apical papilla-derived stem cells. *International Journal of Molecular Sciences*. 2022;23:2615.
30. Sonoyama W, Liu Y, Yamaza T, et al. Characterization of the apical papilla and its residing stem cells from human immature permanent teeth: A pilot study. *Journal of Endodontics*. 2008;34:166–171.
31. Bakopoulou A, About I. Stem cells of dental origin: Current research trends and key milestones towards clinical application. *Stem Cells International*. 2016;2016:4209891.
32. Kim SG. A cell-based approach to dental pulp regeneration using mesenchymal stem cells: A scoping review. *International Journal of Molecular Sciences*. 2021;22:4357.
33. Sequeira DB, Oliveira AR, Seabra CM, et al. Regeneration of pulp-dentin complex using human stem cells of the apical papilla: In vivo interaction with two bioactive materials. *Clinical Oral Investigations*. 2021;25:5317–5329.
34. Araújo PRS, Silva LB, Neto A, et al. Pulp revascularization: A literature review. *The Open Dentistry Journal*. 2017;10:48–56.
35. Zhu H, Guo ZK, Jiang XX, et al. A protocol for isolation and culture of mesenchymal stem cells from mouse compact bone. *Nature Protocols*. 2010;5:550–560.
36. Baksh D, Song L, Tuan RS. Adult mesenchymal stem cells: Characterization, differentiation, and application in cell and gene therapy. *Journal of Cellular and Molecular Medicine*. 2004;8:301–316.
37. Kaneko T, Gu B, Sone PP, et al. Dental pulp tissue engineering using mesenchymal stem cells: A review with a protocol. *Stem Cell Reviews and Reports*. 2018;14:668–676.
38. Azizi SA, Stokes D, Augelli BJ, et al. Engraftment and migration of human bone marrow stromal cells implanted in the brains of albino rats – similarities to astrocyte grafts. *Proceedings of the National Academy of Sciences of the United States of America*. 1998;95:3908–3913.
39. Mathot F, Saffari TM, Rbia N, et al. Functional outcomes of nerve allografts seeded with undifferentiated and differentiated mesenchymal stem cells in a rat sciatic nerve defect model. *Plastic and Reconstructive Surgery*. 2021;148:354–365.
40. Zuk PA, Zhu M, Mizuno H, et al. Multilineage cells from human adipose tissue: Implications for cell-based therapies. *Tissue Engineering*. 2001;7:211–228.
41. Chu DT, Nguyen Thi Phuong T, Tien NLB, et al. Adipose tissue stem cells for therapy: An update on the progress of isolation, culture, storage, and clinical application. *Journal of Clinical Medicine*. 2019;8:917.
42. Fan Y, Hanai JI, Le PT, et al. Parathyroid hormone directs bone marrow mesenchymal cell fate. *Cell Metabolism*. 2017;25:661–672.
43. Murakami M, Hayashi Y, Iohara K, et al. Trophic effects and regenerative potential of mobilized mesenchymal stem cells from bone marrow and adipose tissue as alternative cell sources for pulp/dentin regeneration. *Cell Transplantation*. 2015;24:1753–1765.

44. Liang C, Liang Q, Xu X, et al. Bone morphogenetic protein 7 mediates stem cells migration and angiogenesis: Therapeutic potential for endogenous pulp regeneration. *International Journal of Oral Science*. 2022;14:38.
45. Yang J, Yuan G, Chen Z. Pulp regeneration: Current approaches and future challenges. *Frontiers in Physiology*. 2016;7:58.
46. Levi-Montalcini R, Hamburger V. Selective growth stimulating effects of mouse sarcoma on the sensory and sympathetic nervous system of the chick embryo. *Journal of Experimental Zoology*. 1951;116:321–361.
47. Tomlinson RE, Li Z, Li Z, et al. NGF-TrkA signaling in sensory nerves is required for skeletal adaptation to mechanical loads in mice. *Proceedings of the National Academy of Sciences of the United States of America*. 2017;114:E3632–E3641.
48. Tsutsui TW. Dental pulp stem cells: Advances to applications. *Stem Cells and Cloning: Advances and Applications*. 2020;13:33–42.
49. Gage FH, Batchelor P, Chen KS, et al. NGF receptor reexpression and NGF-mediated cholinergic neuronal hypertrophy in the damaged adult neostriatum. *Neuron*. 1989;2:1177–1184.
50. Liu Z, Wu H, Huang S. Role of NGF and its receptors in wound healing (Review). *Experimental and Therapeutic Medicine*. 2021;21:599.
51. Vega JA, García-Suárez O, Hannestad J, et al. Neurotrophins and the immune system. *Journal of Anatomy*. 2003;203:1–19.
52. Moattari M, Kouchesfehani HM, Kaka G, et al. Evaluation of nerve growth factor (NGF) treated mesenchymal stem cells for recovery in neurotmesis model of peripheral nerve injury. *Journal of Cranio-Maxillofacial Surgery*. 2018;46:898–904.
53. Mizuno N, Shiba H, Xu WP, et al. Effect of neurotrophins on differentiation, calcification and proliferation in cultures of human pulp cells. *Cell Biology International*. 2007;31:1462–1469.
54. Mitsiadis TA, Pagella P. Expression of nerve growth factor (NGF), TrkA, and p75(NTR) in developing human fetal teeth. *Frontiers in Physiology*. 2016;7:338.
55. Liu Q, Lei L, Yu T, et al. Effect of brain-derived neurotrophic factor on the neurogenesis and osteogenesis in bone engineering. *Tissue Engineering Part A*. 2018;24:1283–1292.
56. Cen LP, Ng TK, Liang JJ, et al. Human periodontal ligament-derived stem cells promote retinal ganglion cell survival and axon regeneration after optic nerve injury. *Stem Cells*. 2018;36:844–855.
57. Tauszig-Delamasure S, Bouzas-Rodriguez J. Targeting neurotrophin-3 and its dependence receptor tyrosine kinase receptor C: A new antitumoral strategy. *Expert Opinion on Therapeutic Targets*. 2011;15:847–858.
58. Zhang S, Jin H, Yao L, et al. Neurotrophin-3 enhances the osteogenesis ability of human bone marrow mesenchymal stem cells stimulated by lipopolysaccharide. *Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi* (Chinese Journal of Cellular and Molecular Immunology). 2018;34:47–52.
59. Ji WC, Li M, Jiang WT, et al. Protective effect of brain-derived neurotrophic factor and neurotrophin-3 overexpression by adipose-derived stem cells combined with silk fibroin/chitosan scaffold in spinal cord injury. *Neurological Research*. 2020;42:361–371.
60. Yan Z, Shi X, Wang H, et al. Neurotrophin-3 promotes the neuronal differentiation of BMSCs and improves cognitive function in a rat model of Alzheimer's disease. *Frontiers in Cellular Neuroscience*. 2021;15:629356.
61. Armelin HA. Pituitary extracts and steroid hormones in the control of 3T3 cell growth. *Proceedings of the National Academy of Sciences of the United States of America*. 1973;70:2702–2706.
62. Qian J, Jiayuan W, Wenkai J, et al. Basic fibroblastic growth factor affects the osteogenic differentiation of dental pulp stem cells in a treatment-dependent manner. *International Endodontic Journal*. 2015;48:690–700.
63. Shimabukuro Y, Ueda M, Ozasa M, et al. Fibroblast growth factor-2 regulates the cell function of human dental pulp cells. *Journal of Endodontics*. 2009;35:1529–1535.
64. Kim J, Park JC, Kim SH, et al. Treatment of FGF-2 on stem cells from inflamed dental pulp tissue from human deciduous teeth. *Oral Diseases*. 2014;20:191–204.

65. Forbes BE, Blyth AJ, Wit JM. Disorders of IGFs and IGF-1R signaling pathways. *Molecular and Cellular Endocrinology*. 2020;518:111035.
66. Liu D, Wang Y, Jia Z, et al. Demethylation of IGFBP5 by histone demethylase KDM6B promotes mesenchymal stem cell-mediated periodontal tissue regeneration by enhancing osteogenic differentiation and anti-inflammation potentials. *Stem Cells*. 2015;33:2523–2536.
67. Hao J, Yang H, Cao Y, et al. IGFBP5 enhances the dentinogenesis potential of dental pulp stem cells via JNK and ERK signalling pathways. *Journal of Oral Rehabilitation*. 2020;47:1557–1565.
68. Saito K, Ohshima H. The putative role of insulin-like growth factor (IGF)-binding protein 5 independent of IGF in the maintenance of pulpal homeostasis in mice. *Regenerative Therapy*. 2019;11:217–224.
69. Ahmadi F, Salmasi Z, Mojarad M, et al. G-CSF augments the neuroprotective effect of conditioned medium of dental pulp stem cells against hypoxic neural injury in SH-SY5Y cells. *Iranian Journal of Basic Medical Sciences*. 2021;24:1743–1752.
70. Tsai ST, Chu SC, Liu SH, et al. Neuroprotection of granulocyte colony-stimulating factor for early stage Parkinson's disease. *Cell Transplantation*. 2017;26:409–416.
71. Zhang XM, Du F, Yang D, et al. Granulocyte colony-stimulating factor increases the therapeutic efficacy of bone marrow mononuclear cell transplantation in cerebral ischemia in mice. *BMC Neuroscience*. 2011;12:61.
72. Iohara K, Fujita M, Ariji Y, et al. Assessment of pulp regeneration induced by stem cell therapy by magnetic resonance imaging. *Journal of Endodontics*. 2016;42:397–401.
73. Schmalz G, Widbiller M, Galler KM. Signaling molecules and pulp regeneration. *Journal of Endodontics*. 2017;43:S7–S11.
74. Takeuchi N, Hayashi Y, Murakami M, et al. Similar in vitro effects and pulp regeneration in ectopic tooth transplantation by basic fibroblast growth factor and granulocyte-colony stimulating factor. *Oral Diseases*. 2015;21:113–122.
75. Smojver I, Katalinić I, Bjelica R, et al. Mesenchymal stem cells based treatment in dental medicine: A narrative review. *International Journal of Molecular Sciences*. 2022;23:1662.
76. Moussa DG, Aparicio C. Present and future of tissue engineering scaffolds for dentin-pulp complex regeneration. *Journal of Tissue Engineering and Regenerative Medicine*. 2019;13:58–75.
77. Pinho AC, Fonseca AC, Serra AC, et al. Peripheral nerve regeneration: Current status and new strategies using polymeric materials. *Advanced Healthcare Materials*. 2016;5:2732–2744.
78. Ramachandran N, Singh S, Podar R, et al. A comparison of two pulp revascularization techniques using platelet-rich plasma and whole blood clot. *Journal of Conservative Dentistry*. 2020;23:637–643.
79. Murray PE. Platelet-rich plasma and platelet-rich fibrin can induce apical closure more frequently than blood-clot revascularization for the regeneration of immature permanent teeth: A meta-analysis of clinical efficacy. *Frontiers in Bioengineering and Biotechnology*. 2018;6:139.
80. Xu J, Gou L, Zhang P, et al. Platelet-rich plasma and regenerative dentistry. *Australian Dental Journal*. 2020;65:131–142.
81. Ulusoy AT, Turedi I, Cimen M, et al. Evaluation of blood clot, platelet-rich plasma, platelet-rich fibrin, and platelet pellet as scaffolds in regenerative endodontic treatment: A prospective randomized trial. *Journal of Endodontics*. 2019;45:560–566.
82. Raddall G, Mello I, Leung BM. Biomaterials and scaffold design strategies for regenerative endodontic therapy. *Frontiers in Bioengineering and Biotechnology*. 2019;7:317.
83. Cen L, Liu W, Cui L, et al. Collagen tissue engineering: Development of novel biomaterials and applications. *Pediatric Research*. 2008;63:492–496.
84. Zein N, Harmouch E, Lutz JC, et al. Polymer-based instructive scaffolds for endodontic regeneration. *Materials*. 2019;12:2347.
85. Abbass MMS, El-Rashidy AA, Sadek KM, et al. Hydrogels and dentin-pulp complex regeneration: From the benchtop to clinical translation. *Polymers*. 2020;12:2935.
86. Dayi B, Bilecen DS, Eröksüz H, et al. Evaluation of a collagen-bioaggregate composite scaffold in the repair of sheep pulp tissue. *European Oral Research*. 2021;55:152–161.
87. Li G, Han Q, Lu P, et al. Construction of dual-biofunctionalized chitosan/collagen scaffolds for simultaneous neovascularization and nerve regeneration. *Research*. 2020;2020:2603048.

88. Ouasti S, Donno R, Cellesi F, et al. Network connectivity, mechanical properties and cell adhesion for hyaluronic acid/PEG hydrogels. *Biomaterials*. 2011;32:6456–6470.
89. Ahmadian E, Eftekhari A, Dizaj SM, et al. The effect of hyaluronic acid hydrogels on dental pulp stem cells behavior. *International Journal of Biological Macromolecules*. 2019;140:245–254.
90. Turley EA, Noble PW, Bourguignon LY. Signaling properties of hyaluronan receptors. *Journal of Biological Chemistry*. 2002;277:4589–4592.
91. Yang J, Hsu CC, Cao TT, et al. A hyaluronic acid granular hydrogel nerve guidance conduit promotes regeneration and functional recovery of injured sciatic nerves in rats. *Neural Regeneration Research*. 2023;18:657–663.
92. Issa MM, Köping-Höggård M, Artursson P. Chitosan and the mucosal delivery of biotechnology drugs. *Drug Discovery Today: Technologies*. 2005;2:1–6.
93. Chang B, Ahuja N, Ma C, et al. Injectable scaffolds: Preparation and application in dental and craniofacial regeneration. *Materials Science and Engineering: R: Reports*. 2017;111:1–26.
94. El Ashiry EA, Alamoudi NM, El Ashiry MK, et al. Tissue engineering of necrotic dental pulp of immature teeth with apical periodontitis in dogs: Radiographic and histological evaluation. *Journal of Clinical Pediatric Dentistry*. 2018;42:373–382.
95. Feng X, Lu X, Huang D, et al. 3D porous chitosan scaffolds suit survival and neural differentiation of dental pulp stem cells. *Cellular and Molecular Neurobiology*. 2014;34:859–870.
96. Chávez-Delgado ME, Gomez-Pinedo U, Feria-Velasco A, et al. Ultrastructural analysis of guided nerve regeneration using progesterone- and pregnenolone-loaded chitosan prostheses. *Journal of Biomedical Materials Research Part B: Applied Biomaterials*. 2005;74:589–600.
97. Drury JL, Mooney DJ. Hydrogels for tissue engineering: Scaffold design variables and applications. *Biomaterials*. 2003;24:4337–4351.
98. Li X, Liu T, Song K, et al. Culture of neural stem cells in calcium alginate beads. *Biotechnology Progress*. 2006;22:1683–1689.
99. Poongodi R, Chen YL, Yang TH, et al. Bio-scaffolds as cell or exosome carriers for nerve injury repair. *International Journal of Molecular Sciences*. 2021;22:13347.
100. Benton G, Arnaoutova I, George J, et al. Matrigel: From discovery and ECM mimicry to assays and models for cancer research. *Advanced Drug Delivery Reviews*. 2014;79–80:3–18.
101. Wang J, Chu R, Ni N, et al. The effect of Matrigel as scaffold material for neural stem cell transplantation for treating spinal cord injury. *Scientific Reports*. 2020;10:2576.
102. Luzuriaga J, Irurzun J, Irastorza I, et al. Vasculogenesis from human dental pulp stem cells grown in Matrigel with fully defined serum-free culture media. *Biomedicines*. 2020;8:483.
103. Jeong SY, Lee S, Choi WH, et al. Fabrication of dentin-pulp-like organoids using dental-pulp stem cells. *Cells*. 2020;9:642.
104. Absalan F, Pasandi MS, Ghasemi Hamidabadi H, et al. Matrigel enhances differentiation of human adipose tissue-derived stem cells into dopaminergic neuron. *Neuroscience Letters*. 2021;760:136070.
105. Donato RK, Mija A. Keratin associations with synthetic, biosynthetic and natural polymers: An extensive review. *Polymers*. 2019;12:32.
106. Gao J, Zhang L, Wei Y, et al. Human hair keratins promote the regeneration of peripheral nerves in a rat sciatic nerve crush model. *Journal of Materials Science: Materials in Medicine*. 2019;30:82.
107. Park JY, Yang C, Jung IH, et al. Regeneration of rabbit calvarial defects using cells-implanted nano-hydroxyapatite coated silk scaffolds. *Biomaterials Research*. 2015;19:7.
108. Chen S, Liu S, Zhang L, et al. Construction of injectable silk fibroin/polydopamine hydrogel for treatment of spinal cord injury. *Chemical Engineering Journal*. 2020;399:125795.
109. Liu X, Ma PX. Polymeric scaffolds for bone tissue engineering. *Annals of Biomedical Engineering*. 2004;32:477–486.