

BÖLÜM 6

KÖK HÜCRE ÇEŞİTLERİ VE KAYNAKLARI

Münevver BARAN¹

Kübra Tuğçe KALKAN²

GİRİŞ

Kök hücreler, farklılaşma derecesine göre dört ana hücre tipinde sınıflandırılmaktadır. Bunlar totipotent, pluripotent, multipotent ve unipotent kök hücrelerdir. **Totipotentler**, yumurtanın döllenmesi sırasında oluşan zigot gibi tüm hücre tiplerine farklılaşma yeteneğine sahiptir. Embriyonik kök hücreler, mezoderm ve endodermden türetilen hücreler gibi **pluripotent hücreler**, ne redeyse tüm hücre tiplerine farklılaşma yeteneğine sahiptir. **Multipotent kök hücreler**, kırmızı ve beyaz kan hücreleri veya trombositler haline gelebilen yetişkin kök hücreler olarak ilgili bir hücre ailesine farklılaşma yeteneğine sahiptir. **Unipotent kök hücreler** ise kas kök hücreleri gibi yalnızca kendi tipindeki hücreleri üretme yeteneğindedir.¹⁻³

KÖK HÜCRE ÇEŞİTLERİ

Totipotent Kök Hücreler

Kök hücrelerin sınıflandırılması tipik olarak kökenlerine veya farklılaşma potansiyellerine dayalıdır.² Potansiyelleri bakımından, hiyerarşinin en tepesini, plasenta hücreleri de dahil olmak

üzere tüm hücre tiplerine farklılaşabilen **totipotent** hücreler oluşturur. Kök hücreler arasında en yüksek potansiyele sahip olan totipotent kök hücreler bütün bir embriyo oluşturabilmektedir. İnsan embriyogenesi, bir spermatozoon tarafından döllenmiş bir oositten kaynaklanan totipotent zigotla başlar ve daha sonra blastosiste dönüsür. Blastosist, plasentanın çoğunu oluşturan trofoblast ve uterus dokusunda implantasyonla embriyoya dönüşen iç hücre kütlesinden oluşur.⁴

Pluripotent Kök Hücreler

Pluripotent kök hücreler (PSC), endoderm, mezoderm ve ektoderm dahil olmak üzere in vitro üç germ tabakasını oluşturur. PSC'ler, hemen hemen her hücreye farklılaşabilen, sınırsız kendini yenileme potansiyeline sahip hücrelerdir. Kendini yenileme, hücre döngüsü kontrolü ile ilişkilidir. PSC'lerin hücre döngüsünü kontrol eden benzersiz mekanizmalar vardır; bu mekanizmlar sınırsız çoğalmayı ve farklılaşma kapasitesini destekler.⁵

PSC'ler, erken embriyonik dönemin farklı aşamalarından gelişirler ve kendi kendini yenileme potansiyelini korurlar. Embriyonik kök hücreler (ESC'ler) ve indüklenmiş PSC'ler (iPSC'ler)

¹ Doç. Dr., Erciyes Üniversitesi, Eczacılık Fakültesi, Temel Bilimler AD., munevverbaran@erciyes.edu.tr,
ORCID iD: 0000-0003-0369-1022

² Dr. Öğr. Üyesi, Ahi Evran Üniversitesi, Tıp Fakültesi, Histoloji-Embriyoloji AD., ktugce.kalkan@gmail.com,
ORCID iD: 0000-0001-7461-277X

visi, sinir sistemi hastalıklarında umut verici bir araçtır.^{85,86}

Kadavra kök hücreleri etik çırıltıda olan bir diğer kök hücre kaynağı olarak güncellliğini korumaktadır. Bilim insanları bu tip hücrelerden elde edilen yeni hücrelerin çoğalma hızlarının ölen kişilerin yaşıyla ters orantılı olduğunu bildirmektedir.⁸⁷ Kadavra kök hücreler üzerine yapılan bir çalışmada insan kadavralarındaki beyin hücrelerinden olgunlaşmamış nöral kök hücrelerinin izole edildiği rapor edilmiştir.⁸⁸ Farklı bir çalışmada kadavranın vasküler dokularının, insan kadavra mezenkimal kök hücrelerinin alternatif bir kaynağı olduğu tespit edilmiştir.⁸⁹

İn vitro üretilen kök hücrelerin terapötik bir ajan olarak kullanıldığı klinik araştırmaların sayısı günümüzde hızla artmaktadır. Rejeneratif tıp alanında, çok sayıda hastalık, çeşitli farmakolojik veya kimyasal ajanların kök hücreleri nasıl etkileşidine dair araştırmaların odak noktasıdır.⁹⁰

KAYNAKLAR

- Prządka P, Buczak K, Frejlich E, Gąsior L, Suliga K, Kiebowicz Z. The role of mesenchymal stem cells (MSCs) in veterinary medicine and their use in musculoskeletal disorders. *Biomolecules*. 2021;11(8):1141.
- Vikartovska Z, Humenik F, Maloveska M, Farbáková J, Hornáková L, Murgoci A-N, et al. Adult stem cells based therapies in veterinary medicine. *Archives Vet Sci Med*. 2020;3(2):40–50.
- Kalra K, Tomar PC. Stem cell: basics, classification and applications. *Am J Phytomed Clin Therapeut*. 2014;2(7):919–930.
- Mohammad H, Ghazimoradi, Ali Khalafizadeh, Sadegh Babashah, A critical review on induced totipotent stem cells: Types and methods, *Stem Cell Research*, Volume 63, 2022, 102857.
- Varzideh F, Gambardella J, Kansakar U, Jankauskas SS, Santulli G. Molecular Mechanisms Underlying Pluripotency and Self-Renewal of Embryonic Stem Cells. *Int J Mol Sci*. 2023 May 7;24(9):8386.
- Dekel C, Morey R, Hanna J, Laurent LC, Ben-Yosef D, Amir H. Stabilization of hESCs in two distinct substances along the continuum of pluripotency. *iScience*. 2022; 25:105469.
- Plusa B, Hadjantonakis A.-K. Embryonic stem cell identity grounded in the embryo. *Nature*. 2014; 16:502–504.
- Varzideh F, Mone P, Santulli G. Bioengineering Strategies to Create 3D Cardiac Constructs from Human Induced Pluripotent Stem Cells. *Bioengineering*. 2022; 9:168.
- Schmidt R, Plath K. The roles of the reprogramming factors Oct4, Sox2 and Klf4 in resetting the somatic cell epigenome during induced pluripotent stem cell generation. *Genome Biol*. 2012; 13:251.
- Dalton S. Signaling networks in human pluripotent stem cells. *Curr. Opin. Cell Biol*. 2013; 25:241–246.
- George MN, Leavens KE, Gadue P. Genome Editing Human Pluripotent Stem Cells to Model β-Cell Disease and Unmask Novel Genetic Modifiers. *Front. Endocrinol*. 2021; 12:682625.
- Posabella A, Alber AB, Undeutsch HJ et al. Derivation of Thyroid Follicular Cells from Pluripotent Stem Cells: Insights from Development and Implications for Regenerative Medicine. *Front. Endocrinol*. 2021; 12:666565.
- Yilmaz A, Benvenisty N. Defining human pluripotency. *Cell Stem Cell*. 2019; 25:9–22.
- Yamanaka S. Pluripotent stem cell-based cell therapy—promise and challenges. *Cell Stem Cell*. 2020; 27:523–531.
- Kansu E. Kök hücre biyolojisi ve plastisitesinde güncel kavramlar. *ANKEM Dergisi*, 2006; 20(ek-2):1-8.
- Moore KA, Ema H, Lemischka IR. In vitro maintenance of highly purified, transplantable hematopoietic. *Stem Cells Blood*, 1997; 89 (12) :4337-47.
- Kimbrel EA, Lanza R. Next-generation stem cells- ushering in a new era of cell-based therapies. *Nat Rev Drug Discov*. 2020; 19:463–479.
- Zakrzewski W, Dobrzański M, Szymonowicz M, Rybak Z. Stem cells: past, present, and future. *Stem Cell Res Ther*. 2019 Feb 26;10(1):68.
- Rosner M, Horer S, Feichtinger M, Hengstschläger M. Multipotent fetal stem cells in reproductive biology research. *Stem Cell Res Ther*. 2023 Jun 7;14(1):157.
- Kolios G, Moodley Y. Introduction to Stem Cells and Regenerative Medicine. *Respiration*. 2013;85(1):3-10.
- Bandhavkar S. Stem Cells: An Answer to Treat Neurodegeneration. *Brain Disord Ther*, 2015; 4(194):2.
- Mahla RS. Stem cells applications in regenerative medicine and disease therapeutics. *International journal of cell biology*. 2016; 2016.
- Ungkanont A, Mongkonsritrakoon W, Jootar S, Sriachikul T. Allogeneic stem cell transplantation in a patient with refractory burkitt's lymphoma using non-myeloablative conditioning regimen. *Bone marrow transplantation*. 2000;26 (12):1351-1354.
- Berebichez-Fridman R, Montero-Olvera PR. Sources and clinical applications of mesenchymal stem cells: state-of-the-art review. *Sultan Qaboos Univ. Med. J*. 2018;18, e264–e277.
- Çerçi E, Erdost H. Adipose tissue derived mesenchymal stem cells from rat with non-enzymatic isolation method. *CBU-SBED*, 2016;3(2):299–302.
- Kahraman S, Candan ZN. İnsan embriyonik kök hücreleri. *Türkiye Klinikleri J Surg Med.Sci*, 2006; 43:21-5.
- Reubinoff BE, Pera MF, Fong CY, Trounson A, Bongso A. Embryonic stem cell lines from human blastocysts: somatic differentiation in vitro. *Nat. Biotechnol*. 2000; 18:399–404.
- Lakshminarayanan A. Differentiating ability of Stem cells-A Mini Review. *Sree Balaji Journal of Biomedical Sciences*, 2022;1(2).

29. Takahashi K, Tanabe K, Ohnuki, M, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell* 2007; 131:861-872.
30. Neganova I, Lako M. G1 to S phase cell cycle transition in somatic and embryonic stem cells. *J. Anat.* 2008;213(1):30-44.
31. Liu QW, Huang QM, Wu HY, et al. Characteristics and Therapeutic Potential of Human Amnion-Derived Stem Cells. *Int J Mol Sci.* 2021;22(2):1-33.
32. Hoogduijn MJ. Are mesenchymal stromal cells immune cells? *Arthritis Res Ther* 2015; 17:88.
33. Ding DC, Shyu WC, Lin SZ. Mesenchymal stem cells. *Cell Transplant.* 2011;20(1):5-14.
34. Sidhu K.S. Neurodegenerative Diseases Stem Cell-based Therapeutic: A Perspective. *Journal of Neurology and Neuroscience*, 2016;7(1):75-82.
35. Krause D. Plasticity of marrow-derived stem cells. *Gene Ther.* 2002; 9:754-758.
36. Çerci E, Erdost H. Kök Hücre. *Atatürk Üni Veteriner Bilimleri Dergisi*. 2019; 14(2): 221-228
37. Kaya MM, Tutun H. "Kök Hücre Üretimi, İzolasyonu ve Tedavide Kullanımı." *Veteriner Farmakoloji ve Toksikoloji Derneği Bülteni*. 2021;12.(2):55-78.
38. Hida N, Nishiyama N, Miyoshi S et al. Novel cardiac precursor-like cells from human menstrual blood-derived mesenchymal cells. *Stem Cells*. 2008; 26:1695-1704.
39. Vasanthan J, Gurusamy N, Rajasingh S et al. 2021. Role of human mesenchymal stem cells in regenerative therapy. *Cells*.
40. Gopalarethnam J, Nair AP, Iyer M, Vellingiri B, Subramaniam MD. Advantages of mesenchymal stem cell over the other stem cells. *Acta Histochemica*, 2023;125(4):152041.
41. Lin H, Sohn J, Shen H, Langhans MT, Tuan RS. Bone marrow mesenchymal stem cells: Aging and tissue engineering applications to enhance bone healing. *Biomaterials* 2018; 203:96-110.
42. Han Y, Li X, Zhang Y, Han Y, Chang F, Ding J. Mesenchymal stem cells for regenerative medicine. *Cells*, 2019;8(8):886.
43. Ullah I, Subbarao RB, Rho GJ. Human mesenchymal stem cells – current trends and future prospective. *Biosci. Rep.* 2015; 35:e00191.
44. Ball LM, Bernardo ME, Roelofs H, et al. Multiple infusions of mesenchymal stromal cells induce sustained remission in children with steroid-refractory, grade III-IV acute graft-versus-host disease. *Br J Haematol.* 2013; 163:501-509.
45. Brink L, Grandella C, Mummery CL, Davis RP. Inherited cardiac diseases, pluripotent stem cells and genome editing combined - the past, present and future. *Stem Cells*. 2019;38(2):174-186.
46. Hass R, Kasper C, Böhm S, Jacobs R. Different populations and sources of human mesenchymal stem cells (MSC): A comparison of adult and neonatal tissue-derived MSC. *Cell Communication and Signaling*. 2011;9(1):1-14.
47. Can A. Haematopoietic stem cells niches: interrelations between structure and function. *Transfus Apher Sci*. 2008; 38:261-8.
48. Durand C, Dzierzak E. Embryonic beginnings of adult hematopoietic stem cells. *Haematologica* 2005; 90:100-8.
49. Elgun E, Gürsoy V, Ersal T, Pinar İE, Özkalımkas F, Ozkoacaman V. Relaps/Refrakter Hodgkin Lenfoma Hastalarının Otolog Hematopoetik Kök Hücre Nakil Sonuçları ve Risk Faktörü Etkilerinin Retrospektif Değerlendirilmesi. *Uludağ Üniversitesi Tip Fakültesi Dergisi*. 2022;48(2):231-237.
50. Seita J, Weissman IL. Hematopoietic stem cell: self-renewal versus differentiation. *Wiley Interdisciplinary Reviews: Systems Biology and Medicine*. 2010;2(6):640-653.
51. Poliwoda S, Noor N, Downs E et al. Stem cells: a comprehensive review of origins and emerging clinical roles in medical practice. *Orthopedic Reviews*, 2022;14(3):37498.
52. Karakukcu M, Unal E. Stem cell mobilization and collection from pediatric patients and healthy children. *Transfus Apher Sci*. 2015;53(1):17-22.
53. Salazar-Riojas R, Garcia-Lozano JA, Valdes-Galvan M, et al. Effective collection of peripheral blood stem cells in children weighing 20 kilogram or less in a single large-volume apheresis procedure. *J Clin Apher*. 2015;30(5):281-7.
54. Naji A, Eitoku M, Favier B, Deschaseaux F, Rouas-Freiss N, Suganuma N. Biological functions of mesenchymal stem cells and clinical implications. *Cell. Mol life Sci. CMLS* 2019; 76:3323-3348.
55. van Harmelen V, Röhrig K, Hauner H. Comparison of proliferation and differentiation capacity of human adipocyte precursor cells from the omental and subcutaneous adipose tissue depot of obese subjects. *Aktuelle Ernährungsmedizin*, 2003;28(05):101.
56. Ong WK, Sugii S. Adipose-derived stem cells: fat-tissue potentials for therapy. *Int J Biochem Cell Biol*. 2013;45(6):1083-1086.
57. Mazini L, Rochette L, Amine M, Malka G. Regenerative Capacity of Adipose Derived Stem Cells (ADSCs), Comparison with Mesenchymal Stem Cells (MSCs). *IJMS*. 2019;20(10):2523.
58. Dave SD, Vanikar AV, Trivedi HL, Thakkar UG, Gopal SC, Chandra T. Novel therapy for insulin-independent diabetes mellitus: infusion of in vitro generated insulin-secreting cells. *Clin Exp Med*. 2015;15(1):41-45.
59. Zhou W, Lin J, Zhao K, et al. Single-Cell Profiles and Clinically Useful Properties of Human Mesenchymal Stem Cells of Adipose and Bone Marrow Origin. *Am J Sports Med*. 2019;47(7):1722-1733.
60. Qiu C, Ge Z, Cui W, Yu L, Li J. Human Amniotic Epithelial Stem Cells: A Promising Seed Cell for Clinical Applications. *IJMS*. 2020;21(20):1-26.
61. Ding C, Zou Q, Wang F, et al. Human amniotic mesenchymal stem cells improve ovarian function in natural aging through secreting hepatocyte growth factor and epidermal growth factor. *Stem Cell Research and Therapy*. 2018;9(1):1-11.
62. Evans MA, Lim R, Kim HA, et al. Acute or Delayed Systemic Administration of Human Amnion Epithelial Cells Improves Outcomes in Experimental Stroke. *Stroke*. 2018;49(3):700-709.

63. Arutyunyan I, Elchaninov A, Makarov A, Fatkhudinov T. Umbilical cord as prospective source for mesenchymal stem cell-based therapy. *Stem cells international*, 2016;2016:6901286.
64. Jin HJ, Bae YK, Kim M et al. Comparative analysis of human mesenchymal stem cells from bone marrow, adipose tissue, and umbilical cord blood as sources of cell therapy. *International journal of molecular sciences*, 2013;14(9):17986-18001.
65. Mayani H. Biological differences between neonatal and adult human hematopoietic stem/progenitor cells. *Stem Cells Dev*. 2010; 19:285-98.
66. Felli N, Cianetti L, Pelosi E, et al. Hematopoietic differentiation: a coordinated dynamical process towards attractor stable states. *BMC Syst Biol*. 2010; 4:85.
67. Nagamura-Inoue T, He H. Umbilical cord-derived mesenchymal stem cells: their advantages and potential clinical utility. *World journal of stem cells*, 2014;6(2):195.
68. Pipino C, Shangaris P, Resca E, et al. Placenta as a reservoir of stem cells: an underutilized resource? *British medical bulletin*, 2013;105(1).
69. Oliveira MS, Barreto-Filho JB. Placental-derived stem cells: culture, differentiation and challenges. *World journal of stem cells*, 2015;7(4):769.
70. Antoniadou E, David AL. Placental stem cells. *Best Practice & Research Clinical Obstetrics & Gynaecology*. 2016; 31:13-29.
71. Delo DM, De Coppi P, Bartsch G, et al. Amniotic fluid and placental stem cells, *Methods Enzymol*, 2006;419:426-38.
72. Parolini O, Caruso M. Review: Preclinical studies on placenta-derived cells and amniotic membrane: an update. *Placenta*. 2011;32(2):186-195.
73. Moore MC, Van De Walle A, Chang J, Juran C, McFetridge PS. Human Perinatal-Derived Biomaterials, *Advanced Healthcare Materials*, 2017;6(18)1700345.
74. Roy A, Mantay M, Brannan C, Griffiths S. Placental tissues as biomaterials in regenerative medicine. *BioMed Research International*, 2022;2022:6751456.
75. Ohnuki M, Takahashi K. Present and future challenges of induced pluripotent stem cells. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 2015;370(1680): 20140367.
76. Mohamed EAH, Habib SAA. review on Stem Cell Therapy for Diabetes Type 1 and Risk Factors. *International Journal of Pharmaceutical Research and Applications* 2023;8(1):2421-2435.
77. Huangfu D, Osafune K, Maehr R et al. Induction of pluripotent stem cells from primary human fibroblasts with only Oct4 and Sox2, *Nat. Biotechnol*. 2008;26(11):1269-1275.
78. Yamanaka S. A fresh look at iPS cells. *Cell*. 2009; 137:13-17.
79. Atkinson SP. A Preview of Selected Articles. *Stem Cells Transl Med*. 2019; 8:871-873.
80. Kern S, Eichler H, Stoeve J, Klüter H, Bieback K. Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue. *Stem Cells*. 2006; 24:1294-301.
81. Rebelatto CK, Aguiar AM, Moretão MP, et al. Dissimilar differentiation of mesenchymal stem cells from bone marrow, umbilical cord blood, and adipose tissue. *Exp Biol Med (Maywood)*. 2008; 233:901-13.
82. Harris DT. Stem cell banking for regenerative and personalized medicine. *Biomedicines*. 2014; 2:50-79.
83. Boese AC, Le QSE, Pham D, Hamblin MH, Lee JP. Neural stem cell therapy for subacute and chronic ischemic stroke. *Stem cell research & therapy*. 2018;9(1):1-17.
84. Okano H, Temple S. Cell types to order: temporal specification of CNS stem cells. *Curr Opin Neurobiol*. 2009; 19:112-119.
85. Zhao X, Moore D L. Neural stem cells: developmental mechanisms and disease modeling. *Cell and tissue research*, 2018;371:1-6.
86. Tang Y, Yu P, Cheng L. Current progress in the derivation and therapeutic application of neural stem cells. *Cell death & disease*, 2017;8(10): e3108-e3108.
87. Sağsoz H, Ketani MA. Kök Hücreler. *Dicle Üniversitesi Veteriner Fakültesi Dergisi*. 2008; 2:29-33.
88. López JC. Crystal-Clear Glia – Neuron Interactions. *Nature Review Neuroscience*. 2001;2(6):380.
89. Valente S, Alviano F, Ciavarella C, Buzzi M, Ricci F, Tazzari PL, Pasquinelli G. Human cadaver multipotent stromal/stem cells isolated from arteries stored in liquid nitrogen for 5 years. *Stem cell research & therapy*. 2014;5(1):8.
90. Christ GJ, Saul JM, Furth ME, Andersson KE. The pharmacology of regenerative medicine. *Pharmacol Rev*, 2013;65:1091-1133.