BÖLÜM 4

Hücre Döngüsü, Bölünmeler ve Sinyal Sistemleri

Dr. Öğ. Üyesi Ayşe Banu DEMİR[1]
Prof. Dr. Mürvet HAYRAN[2]
Prof. Dr. Sevinç İNAN[3]

GİRİŞ

Yapısında genetik materyali taşıyan, belirli olgunluk ve büyüklüğe ulaşan ökaryotik hücreler, büyüme, çoğalma ve dokuların yenilenmesi amacıyla bölünürler**.** Hücre bölünmesi, hücrenin tüm bileşenlerini tam olarak içeren yeni hücrelerin oluşmasını sağlamak üzere gerçekleşir. Birbirini izleyen iki bölünme arasında gözlenen düzenli ve sistematik süreç **hücre döngüsü** olarak tanımlanır. Bu sürecin evreleri olan; makromolekülerin sentezi ile hücre büyümesi, DNA replikasyonu ve genetik materyalin hücrelere eşit olarak dağılması, hücre döngüsünü kontrol eden moleküler mekanizmalar ile düzenlenir. Hücreler genel olarak büyüdükçe bölünmek durumunda kalırlar. Bölünme hızı, her canlıda ve aynı canlının farklı doku hücrelerinde değişiklik gösterir. Hücre büyüdükçe, hücrenin hacmi yarıçapın küpü oranında artarken, hücre yüzeyi yarıçapın karesi olarak artar, böylece büyüyen bir hücrede hacim, yüzeyden daha fazla artmış olur. Hücrenin yüzeyi, hücrenin yaşamı için gerekli olan oksijen ile besin alış verişini ve artık maddelerin uzaklaştırılmasını sağlayamayacak büyüklüğe ulaşır. Aynı zamanda, büyüyen hücrede sitoplazma/çekirdek oranının artması ile çekirdeğin kontrol etkinliği azalır. Hücre bu süreçte, hücre yüzeyini arttırmak ve hacmini azaltmak, yaşamını sürdürebilmek ve ölümünü engellemek amacıyla çekirdekten bölünme emrinin gelmesi ile bölünür. Her hücre mevcut olan diğer bir hücrenin bölünmesi ile oluşur.

Çok hücreli canlılarda başlıca mitoz ve mayoz bölünme olmak üzere iki tip hücre bölünmesi vardır. Mitoz bölünme; bölünme yeteneği olan somatik hücrelerde görülen, hücre yenilenmesini ve sayısını arttırmayı amaçlayan bölünme şeklidir. Farklılaşmadan önce çoğu ökaryotik hücre, art arda tekrarlayan büyüme için gerekli makromoleküllerin sentezi ve bölünme süreçle-

[1] İzmir Ekonomi Üniversitesi, Tıp Fakültesi, Tıbbi Biyoloji AD
[2] İzmir Ekonomi Üniversitesi Tıp Fakültesi Anatomi AD
[3] İzmir Ekonomi Üniversitesi, Tıp Fakültesi, Histoloji ve Embriyoloji AD

KAYNAKLAR

Alberts B, Johnson A, Lewis J, Morgan D, Raff M, Roberts K, Walter P. Molecular biology of the cell. Garland Science, Taylor & Francis group, 6th Ed, 2015

Alberts B, Johnson A, Lewis J, Morgan D, Raff M, Roberts K, Walter P. Molecular Biology of the cell. Sixth Edition, Garland Science, The cell cycle, Chapter 17, 2015; 963-1020.

Aşan E, Dağdeviren A. Moleküler Histoloji Hücre, Atlas kitapçılık, 2012, 169-192.

Aesoy R, Muwonge H, Asrud KS, Sabir M, Witsoe SL, Bjornstad R, Kopperud RK, Hoivik EA, Doskeland SO, Bakke M. Deletion of exchange proteins directly activated by cAMP (Epac) causes defects in hippocampal signaling in female mice. PLoS One. 2018; Jul 26;13(7):e0200935.

Ayabe H, Anada T, Kamoya T, Sato T, Kimura M, Yoshizawa E, Kikuchi S, Ueno Y, Sekine K, Camp JG, Treutlein B, Ferguson A, Suzuki O, Takebe T, Taniguchi H. Optimal Hypoxia Regulates Human iPSC-Derived Liver Bud Differentiation through Intercellular TGFB Signaling. Stem Cell Reports. 2018; Aug 14;11(2):306-316.

Baliga RS, Preedy MEJ, Dukinfield MS, Chu SM, Aubdool AA, Bubb KJ, Moyes AJ, Tones MA, Hobbs AJ. Phosphodiesterase 2 inhibition preferentially promotes NO/guanylyl cyclase/cGMP signaling to reverse the development of heart failure. Proc Natl Acad Sci U S A. 2018; Jul 31;115(31):E7428-E7437.

Basson MA. Signaling in Cell Differentiation and Morphogenesis. Cold Spring Harb Perspect Biol. 2012 Jun; 4 (6): a008151.

Bertoli C, Skotheim JM, de Bruin RAM. Control of cell cycle transcription during G1 and S phases. Nature Reviews, Molecular Cell Biology, 2013; 14,518-528.

Cavodeassi F, Creuzet S, Etchevers HC. The hedgehog pathway and ocular developmental anomalies. Hum Genet. 2018 Aug 2.

Cavodeassi F, Creuzet S, Etchevers HC. The hedgehog pathway and ocular developmental anomalies. Hum Genet. 2018; Aug 2. da Costa MC, Trentin AG, Calloni GW.FGF8 and Shh promote the survival and maintenance of multipotent neural crest progenitors. Mech Dev. 2018 Jul 31: pii: S0925-4773 (18) 30054-6

Chapman DL, Wolgemuth DJ. Identification of a mouse B-type cyclin which exhibits developmentally regulated expression in the germ line. Mol Reprod Dev. 1992; 33(3):259-269.

Ciemerych MA, Kenney AM, Sicinska E, ve ark. Development of mice expressing a single D-type cyclin. Genes Dev. 2002; 16(24):3277- 3289.

Dalton S. Linking the cell cycle to cell fate decisions, Trends in cell Biology,2015; 25:10,592-600.

Duzagac F, Inan S, Ela Simsek F, Acikgoz E, Guven U, Khan SA, Rouhrazi H, Oltulu F, Aktug H, Erol A, Oktem G. JAK/STAT pathway interacts with intercellular cell adhesion molecule (ICAM) and vascular cell adhesion molecule (VCAM) while prostate cancer stem cells form tumor spheroids. J BUON. 2015 Sep-Oct; 20(5): 1250-7.

Draviam VM, Orrechia S, Lowe M, Pardi R, Pines J. The localization of human cyclins B1 and B2 determines CDK1 substrate specificity and neither enzyme requires MEK to disassemble the Golgi apparatus. J Cell Biol. 2001; 152(5):945-958.

Ekizceli G, Inan S, Oktem G, Onur E, Ozbilgin K. Assessment of mTOR pathway molecules during implantation in rats. Biotech Histochem. 2017 92(6): 450-458.

Fantl V, Stamp G, Andrews A, Rosewell I, Dickson C. Mice lacking cyclin D1 are small and show defects in eye and mammary gland development. Genes Dev. 1995; 9(19):2364-2372.

Gallant P, Nigg EA. Identification of a novel vertebrate cyclin: cyclin B3 shares properties with both A- and B-type cyclins. EMBO J. 1994; 13(3):595-605.

Geng Y, Yu Q, Sicinska E, ve ark. Cyclin E ablation in the mouse. Cell. 2003; 114(4):431-443.

Gnipp S, Mergia E, Puschkarow M, Bufe A, Koesling D, Peters M. Nitric oxide dependent signaling via cyclic GMP in dendritic cells regulates migration and T-cell polarization. Sci Rep 2018; Jul 20;8(1):10969.

Gungorduk K, Ertas IE, Sahbaz A, Ozvural Gungorduk K, Ertas IE, Sahbaz A, Ozvural S, Sarica Y, Ozdemir A, Sayhan S, Gokcu M, Yilmaz B, Sanci M, Inan S, Harma M, Yildirim Y. Immunolocalization of ERK1/2 and p-AKT in normal endometrium, endometrial hyperplasia, and early and advanced stage endometrioid endometrial adenocancer and their prognostic significance in malignant group. Eur J Obstet Gynecol Reprod Biol. 2014 Aug; 179:147-52.

Harashima H, Dissmeyer N, Schnittger A. Cell cycle control across the eucaryotic kingdom. Trends in Cell Biology, 2013; 23:7,345-356.

Hu Frisk JM, Kjellen L, Melo FR, Öhrvik H, Pejler G. Mitogen-Activated Protein Kinase Signaling Regulates Proteoglycan Composition of Mast Cell Secretory Granules. Front Immunol., 2018; Jul 19;9:1670.

Hu Y, Zhou L, Zhu X, Dai D, Bao Y, Qiu Y. Pharmacophore modeling, multiple docking and molecular dynamics studies on Wee1 kinase inhibitors. J Biomol Struct Dyn. 2018; Jul 27:1-25.

Huard JM, Forster CC, Carter ML, Sicinski P, Ross ME. Cerebellar histogenesis is disturbed in mice lacking cyclin D2. Development. 1999; 126(9):1927-1935.

Huston RB, Krebs EG. Activation of skeletal muscle phosphorylase kinase by calcium ions. II. Identification of the kinase activating factor as a proteolytic enzyme. Biochemistry. 1968; 7,6, 2116-2122.

Inan S, Vatansever S, Celik-Ozenci C, Sanci M, Dicle N, Demir Immunolocalizations of VEGF, its receptors flt-1, KDR and TGF-beta's in epithelial ovarian tumors. Histol Histopathol. 2006 Oct;21(10):1055-64.

Jackman M, Firth M, Pines J. Human cyclins B1 and B2 are localized to strikingly different structures: B1 to microtubules, B2 primarily to the Golgi apparatus. EMBO J. 1995; 14(8):1646-1654.

Jiao X, Ke H, Qin Y, Chen ZJ. Molecular Genetics of Premature Ovarian Insufficiency. Trends Endocrinol Metab. 2018; Aug 2.

Jones EY. Understanding cell signalling systems: paving the way for new therapies. Philos Trans A Math Phys Eng Sci. 2015; Mar 6: 373 (2036).

Julian LM,Carpenedo RL, Rothberg JLM, Stanford WL. Formula G1: Cell cycle in the driver's seat of stem cell fate determination. Bioessays. 2016; 38,325-332.

Junqueira's Basic Histology Text and Atlas, McGraw Hill Medical, 14th Edition, Chapter 3, 2016.

Kabeya T, Qiu S, Hibino M, Nagasaki M, Kodama N, Iwao T, Matsunaga T. cAMP signaling promotes the differentiation of human induced pluripotent stem cells into intestinal epithelial cells. Drug Metab Dispos., 2018; Aug 1. pii: dmd.118.082123.

Kierszenbaum AL, Tres L. Histology and Cell Biology : An Introduction to Pathology 4th Ed. Canada: Elsevier; 2015. p.85-104.

Kierszenbaum AL. Histology and Cell Biology: An Introduction to Pathology. Mosby, Inc, 2016; 40-50.

Kowalczyk A, Filipkowski RK, Rylski M, ve ark. The critical role of cyclin D2 in adult neurogenesis. *J* Cell Biol. 2004; 167(2):209-213.

Kozar K, Ciemerych MA, Rebel VI, ve ark. Mouse development and cell proliferation in the absence of D-cyclins. Cell. 2004; 118(4):477-491.

Li J, Li X, Bi H, Ma K, Li B. Developmental Exposure to Atrazine Impairs Spatial Memory and Downregulates the Hippocampal D1 Dopamine Receptor and cAMP-Dependent Signaling Pathway in Rats. Int J Mol Sci. 2018; Jul 31;19(8). pii: E2241.

Li C, Diao F, Qiu D, Jiang M, Li X, Han L, Li L, Hou X, Ge J, Ou X, Liu J, Wang Q. Histone methyltransferase SETD2 is required for meiotic maturation in mouse oocyte. J Cell Physiol. 2018; Aug 5.

Liu X, Zhao T, Bai X, Li M, Ren J, Wang M, Xu R, Zhang S, Li H, Hu Y, Xie L, Zhang Y, Yang L, Yan C, Zhang Y. LOC101930370/MiR-1471 Axis Modulates the Hedgehog Signaling Pathway in Breast Cancer. Cell Physiol Biochem. 2018; 48(3):1139-1150.

Locatelli P, Gimenez CS, Vega MU, Crottogini A, Belaich MN. Targeting the cardiomyocyte cell cycle for heart regeneration. Curr Drug Targets, 2018; Aug 1.

Lozano JC, Perret E, Schatt P, Arnould C, Peaucellier G, Picard A. Molecular cloning, gene localization, and structure of human cyclin B3. Biochem Biophys Res Commun. 2002; 291(2):406-413.

Lundberg AS, Weinberg RA. Functional inactivation of the retinoblastoma protein requires sequential modification by at least two distinct cyclin-cdk complexes. Mol Cell Biol. 1998; 18(2):753-761.

Min J, Feng Q, Liao W, Liang Y, Gong C, Li E, He W, Yuan R, Wu L. IFITM3 promotes hepatocellular carcinoma invasion and metastasis by regulating MMP9 through p38/MAPK signaling. FEBS Open Bio. 2018; Jun 28;8(8):1299-1311.

Moore KL, Persaud TVN, Torchia MG. The Developing Human : Clinically Oriented Embryology Tenth Edition, Elsevier, 2016; 11-17.

Moore KL, Persaud TV, Torchia MG. The Developing Human: Clinically Oriented Embryology. 9th ed. Philadelphia: Saunders; 2013.

Nguyen TB, Manova K, Capodieci P, ve ark. Characterization and expression of mammalian cyclin B3, a prepachytene meiotic cyclin. J Biol Chem. 2002; 277(44):41960-41969.

Ookata K, Hisanaga S, Bulinski JC, ve ark. Cyclin B interaction with microtubule-associated protein 4 (MAP4) targets p34cdc2 kinase to microtubules and is a potential regulator of M-phase microtubule dynamics. J Cell Biol. 1995; 128(5):849-862.

Pagano M, Jackson PK. Wagging the dogma; tissue-specific cell cycle control in the mouse embryo. Cell. 2004; 118(5):535-538.

Peng Y, He X, Chen H, Duan H, Shao B, Yang F, Li H, Yang P,Zeng Y,Zheng J, Li Y,Hu J.,Lin L., Teng L. Inhibition of microRNA-299-5p sensitizes glioblastoma cells to temozolomide via the MAPK/ERK signaling pathway. BioSci Rep., 2018; Jul 30. pii: BSR20181051.

Pines J, Hunter T. Human cyclins A and B1 are differentially located in the cell and undergo cell cycle-dependent nuclear transport. J Cell Biol. 1991; 115(1):1-17.

Pogoriler J, Millen K, Utset M, Du W. Loss of cyclin D1 impairs cerebellar development and suppresses medulloblastoma formation. Development. 2006; 133(19):3929-3937.

Robert J. Textbook of Cell Signaling in Cancer. An Educational Approach. Springer; 2015.

Ross MH, Pawlina W. Histology, A Text and Atlas with Correkated Cell and Molecular Biology. Seventh Edition. Wolters Kluwer Health, Chapter 3, 2016; 84-90.

Satyanarayana A, Kaldis P. Mammalian cell-cycle regulation: several Cdks, numerous cyclins and diverse compensatory mechanisms. Oncogene. 2009; 28(33):2925-2939.

Sherr CJ, Roberts JM. CDK inhibitors: positive and negative regulators of G1-phase progression. Genes Dev. 1999; 13(12):1501-1512.

Sicinska E, Aifantis I, Le Cam L, ve ark. Requirement for cyclin D3 in lymphocyte development and T cell leukemias. Cancer Cell. 2003; 4(6):451-461.

Sicinski P, Donaher JL, Geng Y, ve ark. Cyclin D2 is an FSH-responsive gene involved in gonadal cell proliferation and oncogenesis. Nature. 1996; 384(6608):470-474.

Sicinski P, Donaher JL, Parker SB, ve ark. Cyclin D1 provides a link between development and oncogenesis in the retina and breast. Cell. 1995; 82(4):621-630.

Solvason N, Wu WW, Parry D, ve ark. Cyclin D2 is essential for BCR-mediated proliferation and CD5 B cell development. Int Immunol. 2000; 12(5):631-638.

Tanese K, Emoto K, Kubota N, Fukuma M, Sakamoto M. Immunohistochemical visualization of the signature of activated Hedgehog signaling pathway in cutaneous epithelial tumors. J Dermatol. 2018; Jul 23.

Uluer ET, Aydemir I, Inan S, Ozbilgin K, Vatansever HS. Effects of 5-fluorouracil and gemcitabine on a breast cancer cell line (MCF-7) via the JAK/STAT pathway. Acta Histochem. 2012 Nov; 114(7):641-6.

Vasques-Nóvoa F, Laundos TL, Cerqueira RJ, Quina-Rodrigues C, Soares-Dos-Reis R, Baganha F, Ribeiro S, Mendonça L, Gonçalves F, Reguenga C, Verhesen W, Carneiro F, Paiva JA, Schroen B, Castro-Chaves P, Pinto-do-Ó P, Nascimento DS, Heymans S, Leite-Moreira AF, Roncon-Albuquerque R Jr. MicroRNA-155 Amplifies Nitric Oxide/cGMP Signaling and Impairs Vascular Angiotensin II Reactivity in Septic Shock. Crit Care Med., 2018; Sep;46(9):e945-e954.

Valier L. Cell cycle rules pluripotency, Cell Stem Cell,2015; 17:6,131-132.

Waclaw RR, Chatot CL. Patterns of expression of cyclins A, B1, D, E and cdk 2 in preimplantation mouse embryos. Zygote. 2004; 12(1):19-30.

Weinberg RA. The Biology of Cancer. 2nd Ed. Garland Science: Taylor & Francis Group, LLC; 2014.

Wiese KE, Nusse R, van Amerongen R. Wnt signalling: conquering complexity. Development. 2018 Jun 26: 145 (12).

Wu L.,Chen Z., Xing Y. MiR-506-3p inhibits cell proliferation, induces cell cycle arrest and apoptosis in retinoblastoma by directly targeting NEK6. Cell Biol Int, 2018; Aug 6.

Xu Y, Zhu N, Xu W, Ye H, Liu K, Wu F, Zhang M, Ding Y, Zhang C, Zhang H, O'Donnell J, Pan J. Inhibition of Phosphodiesterase-4 Reverses Aβ-Induced Memory Impairment by Regulation of HPA Axis Related cAMP Signaling. Front Aging Neurosci., 2018; Jul 24;10:204.

Xue Q, Bai B, Ji B, Chen X, Wang C, Wang P, Yang C, Zhang R, Jiang Y, Pan Y, Cheng B, Chen J. Ghrelin Through GHSR1a and OX1R Heterodimers Reveals a Gαs-cAMP-cAMP Response Element Binding Protein Signaling Pathway *in Vitro*. Front Mol Neurosci., 2018; Jul 17;11:245.

Youness RA, Assal RA, Motaal AA, Gad MZ. A novel role of sONE/NOS3/NO signaling cascade in mediating hydrogen sulphide bilateral effects on triple negative breast cancer progression. Nitric Oxide. 2018; Aug 4;80:12-23.

Youngblood JL, Coleman TF, Davis SW. Regulation of pituitary progenitor differentiation by β-catenin. Endocrinology. 2018; Sep 1;159(9):3287-3305.

Zeng X, Ju D. Hedgehog Signaling Pathway and Autophagy in Cancer. Int J Mol Sci. 2018; Aug 3;19(8). pii: E2279.

Zeren T, Inan S, Seda Vatansever H, Ekerbicer N, Sayhan S. Significance of tyrosine kinase activity on malign transformation of ovarian tumors: a comparison between EGF-R and TGF-alpha. Acta Histochem. 2008;110(3):256-63.