TÜMÖR SUPRESSÖR GENLER

25. BÖLÜM

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GENEL ÖZELLİKLER

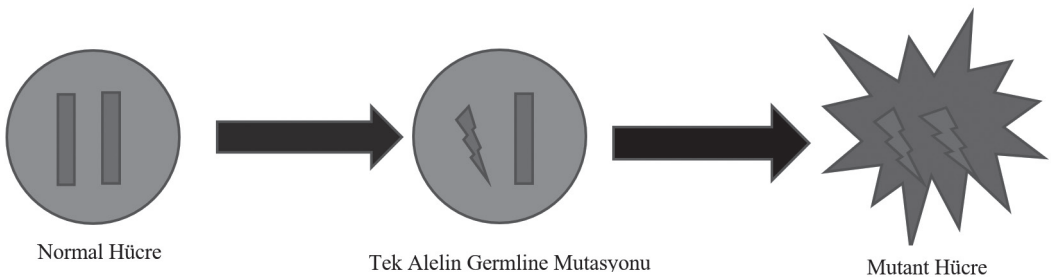
Tümör supressör genlerin ne olduğu ve tümör oluşumunu önlemek için nasıl çalıştıkları konusundaki bilgilerimiz, 1993'te Knudson'un "Anti-onkogenler ve Kanser" adlı makalesi sonrası gelişmeye başlamıştır (1).

Aslında bu çalışmadan önce "tümör baskılama" terimi, kabul gören bir kavramdı. Bu kavram Theodor Boveri'nin "inhibitör kromozomlar" olarak adlandırdığı çalışmalar ile başlar (2).

Günümüzde bilinen asgari 24 tane tümör supressör gen vardır. Tümör supressör genler genetik stabiliteyi korur. Genomun değişime uğramadan devamından sorumludur. Knudson›un kanser oluşumunu açıklamaya yönelik geliştirdiği "çift vuruş" hipotezi (Şekil 1), çoğu tümör supressör gen için hala geçerlidir. Bu hipoteze göre bir tümör supressör genin bir alelinin germline mutasyonu, bireyin yaşamı boyunca meydana gelen ikinci alelin somatik mutasyonu ile tümör oluşumuna yatkınlık sağlar. Bu durum ise yeni bir tümör oluşumunun yolunu açmış olur. Bazı tümör supressör genlerin mutasyonu ise sendromlara yol açar (Tablo 1) (3).

Kinzler ve Vogelstein tarafından, tümör supressör genler 2 kategoriye ayrılmıştır: "gatekeeper denilen bekçi genler" ve "caretakers yani bakıcı genleri" (4). Gatekeeper genler, hücrelerin büyüme veya bölünme döngüleri boyunca nasıl ilerleyeceğini kontrol ederken, caretakers genler genomun bütünlüğünü korur. Bu iki sınıfın klinikteki önemi ise, yeni rejenasyon ilaçların moleküler hedefli olmasıdır. Genellikle kinazlar gibi onkojenlere karşı inhibisyon göstererek bir bakıma tümör supresyonu görevi almaktadırlar. Pasif hale gelmiş tümör supressör genleri yeniden aktif hale getirmeyi amaçlayan birtakım çalışmalar söz konusudur. Bu çalışmalar genellikle tümör supressörleri düzenleyen moleküllere odaklanmış çalışmalardır (5).

Kanserlerin en önemli özelliği DNA hasarına verilen yetersiz cevap ve onarım yolaklarındaki



Şekil 1. Tümör supressör genlerin çift vuruşla inaktive olması

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VHL'nin HIF bağımsız tümör supressör özelikleri de vardır. VHL, en önemli tümör supressör genlerden olan p53 ile de ilişki içindedir. VHL, proteini MDM2 aracılığı ile p53 e direkt bağlanarak ubikitinasyonu baskılar, p53 ü stabilize eder. Ayrıca VHL'nin mikrotübül fonksiyonlarını da düzenlediği, stabilitesini sağladığı da gösterilmiştir (71-73).

VHL sendromu %80 ailesel olarak ortaya çıkmakta ve otozomal dominant olarak kalıtılmaktadır. Sendromlu bireylerde böbrek tümörlerinin görülme yaşı sporadik vakalardan yaklaşık 20 yaş erken gözlenir. Böbrek tümörleri dışında hemanjioblastom, feokromasitoma, pankreasın nöroendokrin tümörleri, epididim kistleri de sıklıkla gözlenir ve genellikle bu hastalarda mortaliteyi belirleyen santral sinr sistemi tümörleri olur (74-76).

VHL sendromu için tanı kriterleri:

- Santral sinir sistemi hemanjioblastomları (retinal olanlar da dahil)
- Renal karsinom
- Nöroendokrin neoplazmlar ya da pankreasta multiple kistler
- Endolemfatik sac tümörleri
- Feokromasitoma, paraganglioma, glomus tümörü (77)

KAYNAKÇA

1. Knudson AG, Antioncogenes and human cancer. *Proc Natl Acad Sci* USA 1993; 90:10914-10921.
2. Salmena L, PTEN: History of a Tumor Suppressor. *Methods Mol Biol* 2016; 1388:3-11.
3. Knudson AG: Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci* USA 1971; 68:820-823.
4. Kinzler KW, Vogelstein B. Cancer-susceptibility genes. Gatekeepers and caretakers. *Nature*. 1997; 386:761, 763.
5. Luc G. T. Morris, Timothy A. Chan. Therapeutic Targeting of Tumor Suppressor Genes *Cancer* 2015; 121(9):1357-68.
6. Ciccia A, Elledge SJ. The DNA damage response: making it safe to play with knives. *Mol Cell* 2010; 40: 179–204.
7. Fung Y.K., Murphree A.L., T'Ang A.. Structural evidence for the authenticity of the human retinoblastoma gene. *Science* 1987; 236 (4809), 1657-1661.
8. Burke, J.R.; Deshong, A.J.; Pelton, J.G. Phosphorylation-induced conformational changes in the Retinoblastoma Protein Inhibit E2F Transactivation Domain Binding. *J. Biol. Chem.* 2010; 285, 16286–16293.
9. Buchkovich, K.; Duffy, L.A.; Harlow, E. The retinoblastoma protein is phosphorylated during specific phases of the cell cycle. *Cell* 1989; 58, 1097–1105.
10. Narasimha, A.M.; Kaulich, M.; Shapiro, G.S. Cyclin D activates the RB tumor suppressor by mono-phosphorylation. *Elife* 2014; 3 :e02872. doi: 10.7554/eLife.02872.
11. Kolupaeva, V.; Janssens, V. PP1 and PP2A phosphatases–cooperating partners in modulating retinoblastoma protein activation. *FEBS J.* 2013; 280, 627–643.
12. Morris, E.J.; Dyson, N.J. Retinoblastoma protein partners. Adv. *Cancer Res*. 2001; 82, 1–54.
13. Ferreira R, Naguibneva I, Pritchard LL. The rb/chromatin connection and epigenetic control: Opinion. *Oncogene*. 2001; 20:3128-3133.
14. Hilgendorf KI, Leshchiner ES, Nedelcu S. The retinoblastoma protein induces apoptosis directly at the mitochondria. *Genes Dev*. 2013; 27:1003-1015.
15. Kitajima S., Li F. Tumor Milieu Controlled by RB Tumor Suppressor *Int. J. Mol. Sci.* 2020; *21*(7), 2450
16. Gupta A, Shah K. Reactivation of p53 gene by MDM2 inhibitors: A novel therapy for cancer treatment . *Biomed Pharmac* 2019; 109:484-92
17. Horn, H.F, Vousden, K.H. Coping with stress: multiple ways to activate p53. *Oncogene 26*, 2007; 1306–1316.
18. Tsai YY, Cheng YW. P53 gene mutation spectrum and the relationship between gene mutation and protein levels in pterygium. *Mol Vis* 2005; 18:11:50-55
19. Levine AJ. p53, the cellular gatekeeper for growth and division. *Cell.* 1997; 88:323–331.
20. Varley JM, Evans DGR, Birch JM. Li-Fraumeni syndrome-a molecular and clinical review, *Brit J Cancer* 1997; 76(1):1- 14.
21. Dai, C., and Gu, W.. p53 post-translational modification: deregulated in tumorigenesis. *Trends Mol. Med*. 2010; 16, 528–536.
22. Liu Y. p53 modifications: exquisite decorations of the powerful guardian J*ournal of Molecular Cell Biology* 2019; 11(7), 564–577
23. Kastenhuber, E.R., Lowe, S.W. Putting p53 in context. *Cell* 2017; *170*, 1062–1078.
24. Basu S Genetic Modifiers of the p53 Pathway. *Cold Spring Harb Perspect Med*. 2016 Apr; 6(4): a026302.
25. Chen WY. Tumor suppressor HIC1 directly regulates SIRT1 to modulate p53-dependent DNA-damage responses. *Cell* 2005; 123: 437-48.
26. Lain S, Hollick JJ, Campbell J. Discovery, in vivo activity, and mechanism of action of a small-molecule p53 activator. *Cancer Cell*. 2008; 13:454-463.
27. Karaman A. Role of the p53 tumor suppressor gene in gastric cancer August *Turkiye Klinikleri Journal of Medical Sciences* **2003;** 23(1):67-73
28. Luc G. T. Therapeutic Targeting of Tumor Suppressor Genes; *Cancer* 2015; 121:1357-68.
29. Komarova EA, Chumakov PM, Gudcov AV. Molecular genetics of cancer. TP53 in cancer origin and treatment. Edited by Cowell JK. 2009; 9:195–221.
30. Vassilev LT, Vu BT. In vivo activation of the p53 pathway by small-molecule antagonists of MDM2. *Science.* 2004; 303:844-848.
31. Joerger, A.C., Fersht, A.R. The p53 pathway: origins, inactivation in cancer, and emerging therapeutic approaches. *Annu. Rev. Biochem.* 2016; *85*, 375–404.
32. Varley JM, Evans DG. Li-Fraumeni syndrome-a molecular and clinical review. *Br J Cancer.* 1997; 76:1–14.

33. Schneider K, Zelley K, Nichols KE. Li-Fraumeni Syndrome Gene Review spmıd:20301488
34. Aedma S.K.; Kasi A. **Li-Fraumeni Syndrome** Last Update: May 22, 2020 PMID: 3033531
35. Guha T, Malkin D. Inherited TP53 Mutations and the Li-Fraumeni Syndrome. *Cold Spring Harb Perspect Med*. 2017; Apr 03;7(4)
36. Liu Y, Tavana O. p53 modifications: exquisite decorations of the powerful guardian *Journal of Molecular Cell Biology* 2019; 11(7), 564–577
37. Chiappori AA, Soliman H. INGN-225: a dendritic cell-based p53 vaccine (Ad.p53-DC) in small cell lung cancer: observed association between immune response and enhanced chemotherapy effect. *Expert Opin Biol Ther.* 2010; 10:983–991
38. Chodosh LA. Expression of BRCA1 and BRCA2 in nor mal and neoplastic cells. *J Mammary Gland Biol Neoplasia* 1998; 3:389-402
39. Varol U. Kucukzeybek Y. BRCA genes: BRCA 1 and BRCA 2 *JBUON* 2018; 23(4): 862-866
40. Lord C.J. Ashworth A. BRCAness revisited. *Nat Rev Cancer.* 2016; 16: 110-120
41. Welcsh PL, King MC. BRCA1 and BRCA2 and the genetics of breast and ovarian cancer. *Hum Mol Genet* 2001; 10(7):705–713.
42. Savage K.I. Gorski J.J. Identification of a BRCA1-mRNA splicing complex required for efficient DNA repair and maintenance of genomic stability. *Mol Cell*. 2014; 54: 445-459
43. Welcsh PL, King MC. BRCA1 and BRCA2 and the genetics of breast and ovarian cancer. *Hum Mol Genet* 2001; 10(7):705–713.
44. Alsop K., Fereday S. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian ovarian cancer study group. *J. Clin. Oncol*. 2012; 30:2654–2663.
45. Antoniou A, Pharoah PD, Narod S. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet* 2003; 72(5):1117–30.10.1086/375033
46. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. *J Clin Oncol* 2007; 25(11):1329–33.10.1200/JCO.2006.09.1066
47. Sanghamitra M., Asmita D. Role of BRCA Mutations in the Modulation of Response to Platinum Therapy *Front Oncol.* 2018; 8: 16.
48. Musolino A, Bella MA. BRCA mutations, molecular markers, and clinical variables in early-onset breast cancer: a population-based study. *Breast* 2007; 16(3):280–92.
49. Nielsen TO, Hsu FD. Immunohistochemical and clinical characterization of the basal-like subtype of invasive breast carcinoma. *Clin Cancer Res* 2004; 10(16):5367–74.
50. Mavaddat N, Barrowdale D. Pathology of breast and ovarian cancers among BRCA1 and BRCA2 mutation carriers: results from the Consortium of Investiga- tors of Modifiers of BRCA1/2 (CIMBA). *Cancer Epidemiol Biomarkers Prev* 2012; 21(1):134–147.
51. Li DM, Sun H. TEP1, encoded by a candidate tumor suppressor locus, is a novel protein tyrosine phosphatase regulated by transforming growth factor beta. *Cancer Res* 1997; 57(11):2124–9.
52. Hollander MC, Blumenthal GM, Dennis PA. PTEN loss in the continuum of common cancers, rare syndromes and mouse models. Nat Rev Cancer 2011; 11(4):289–301.10.1038/nrc3037
53. Stambolic V. Negative regulation of PKB/Akt-dependent cell survival by the tumor suppressor PTEN. *Cell* 1998; 95, 29–39.
54. Leslie NR, Downes CP. PTEN: the down side of PI 3-kinase signalling. *Cell Signal* 2002; 14(4):285–95.
55. Molina AO. PTEN in cancer, metabolism and aging. *Trends Endocrinol Metab*. 2013 Apr; 24(4): 184-9
56. Song MS. The functions and regulation of the PTEN tumour suppressor. *Nat Rev Mol Cell Biol*. 2012; 13:283–296
57. Marsh DJ. Mutation spectrum and genotype-phenotype analyses in Cowden disease and Bannayan-Zonana syndrome, two hamartoma syndromes with germline PTEN mutation. *Hum. Mol. Genet* 7,1998; 507–515.
58. Eng C. PTEN: one gene, many syndromes *Hum Mutat* 2003 Sep;22(3):183-98. PMID: **12938083** DOI: 10.1002/humu.10257
59. Garcia-Junco-Clemente P, Golshani P. PTEN: a master regulator of neuronal structure, function, and plasticity. *Commun Integr Biol* 2014; 7(1):e28358.10.4161/cib.28358
60. Milella M., Falcone I. PTEN: Multiple Functions in Human Malignant Tumors *Front Oncol*. **2015; 5: 24.**
61. Akdeniz D. Tunçer Ş.B. PTEN Gen Yolağı ve Meme Kanseri Arasındaki İlişki *Ankara Üniversitesi Tıp Fakültesi Mecmuası* 2018; 71(2):105-110
62. DeGraffenried LA, Fulcher L,Friedrichs WE. Reduced PTEN expression in breast cancer cells confers susceptibility to inhibitors of the PI3 kinase/ Akt pathway. *Ann Oncol* 2004; 15:1510-1516.
63. Kim WY, Kaelin WG. Role of VHL gene mutation in human cancer. *J Clin Oncol* 2004; 22(24):4991-5004.
64. Yang H, Kaelin WG, Jr.:Molecular pathogenesis of the von Hippel-Lindau hereditary cancer syndrome: Implications for oxygen sensing.*Cell Growth Differ* 2001; 12:447-455.
65. Haase VH. The VHL tumor suppressor: Master regulator of HIF. *Curr Pharm Des* 2009; 15(33):3895-903
66. Clifford SC, Cockman ME et al: contrasting effects on HIF1 alpha regulation by disease-causing pVHL mutationscorrelate with patterns of tumourigenesis in VHL disease. *Hum Mol Genet* 2001;10:1029-1038.
67. Zhang J., Zhang Q. VHL and Hypoxia Signaling: Beyond HIF in Cancer *Biomedicines.* 2018 Mar; 6(1): 35.
68. Brugarolas J. Molecular genetics of clear-cell renal cell carcinoma. *J Clin Oncol*. 2014; 32:1968-76.
69. Demirel H.S., Çınar İ., Von Hıppel-Lındau Tümör Baskılayıcı Genıne Moleküler Yaklaşım *Kocatepe Tıp Dergisi Kocatepe Medical Journal* 2016; 17:136-142
70. Moore L.E., Nickerson M.L., Brennan P., Von hippel-lindau (VHL) inactivation in sporadic clear cell renal cancer: Associations with germline VHL polymorphisms and etiologic risk factors. *PLoS Genet.* 2011; 7:e1002312. doi: 10.1371/journal.pgen.1002312.

71. Roe JS, Kim H, Lee SM., P53 stabilization and trasactivation by a von Hippel-Lindau protein. *Mol Cell* 2006; 22(3):395-405.
72. Hoffman M.A., Ohh M., Yang H.. Von hippel-lindau protein mutants linked to type 2c VHL disease preserve the ability to downregulate hif. *Hum. Mol. Genet.* 2001; 10:1019–1027. doi: 10.1093/hmg/10.10.1019.
73. Gordeuk V.R., Sergueeva A.I., Miasnikova G.Y. Congenital disorder of oxygen sensing: Association of the homozygous chuvash polycythemia VHL mutation with thrombosis and vascular abnormalities but not tumors. *Blood.* 2004; 103:3924–3932. doi: 10.1182/blood-2003-07-2535.
74. Nickerson ML, Jaeger E, Shi Y et al. Improved identification of von Hippel-Lindau gene alterations in clear cell renal tumors. *Clin Cancer Res* 2008;14:4726–34.
75. Choyke PL, Glenn GM, Walther MM et al. Von Hippel-Lindau disease: genetic, clinical, and imaging features. *Radiology* 1995; 194:629–42.
76. Simpson JL, Carson SA, Cisneros P. Preimplantation genetic diagnosis (PGD) for heritable neoplasia. *J Natl Cancer Inst Monogr* 2005 ;34:87–90.
77. Chittiboina P, Lonser RR. Von Hippel Lindau disease. *Handb Clin Neurol* 2015; 132:139-5