7.BÖLÜM

PROSTAT KARSİNOMU VE PROSTAT KARSİNOMUNUN MOLEKÜLER MEKANİZMALARI

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Prostat kanseri (PCa) dünya çapında en sık görülen kanserlerdendir. PCa insidansı da hızla artmaktadır. PCa, insidans ve mortalite oranları büyük oranda popülasyondan popülasyona göre değişmekle birlikte, dünyanın çoğu yerinde erkeklerde en önemli non-kutanöz kanserdir. PCa insidansının dünyanın daha gelişmiş bölgelerinde daha yüksek olduğu bilinmektedir. Bu durumu kısmen tarama ile birlikte erken teşhisin ve tıbbi bakıma erişim oranını daha kolay ve yüksek olması ile açıklayamaya çalışabiliriz. Bununla birlikte, PCa'nun mortalite yüzdelerine baktığımızda, en yüksek mortalitenin Afrika kökenli erkeklerde görüldüğü bildirilmiştir (1). Amerikan kanser istatistik merkezinin son verilerine göre 2019 yılında 174.650 kişinin yeni PCa hastasının olduğu ve 2019 yılında tahmini 31,620 kişinin PCa'dan öldüğü saptanmıştır (2).

Prostat Karsinomlarına Klinik Yaklaşım

PCa riski 50 yaşına kadar düşükken, 50 yaşından sonra yaşla birlikte giderek artmaktadır. Dünya geneline bakıldığında, tüm PCa olgularının yaklaşık dörtte üçü 65 yaş ve üzeri yaşta görülmektedir (1-4). Prostat kanseri etiyolojisine baktığımızda moleküler faktörler, çevresel faktörler, hormonal faktörler ve yaşam şekli olmak üzere birçok faktör rol almaktadır. Moleküler faktörler içinde ise genetik modifikasyonlar, epigenetik modifikasyonlar, altered mikroRNA, sinyal yolakları vardır (Tablo-1).

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çeşitli kanserlerde farklı Ras tipleri saptanmıştır (95). PCa'da ise ras mutasyon oranları oldukça değişken olup batı toplumlarında %5 civarında görülürken Japon toplumunda ras mutasyonu oranı %26'lara kadar çıkmaktadır (96).

BCL-2

Bcl-2 antiapopitotik ve androjen bağımsız bir proteindir. Normal prostat dokusunda bulunmamakla birlikte bcl-2'nin PCa'larının yaklaşık yarısında eksprese edildiği gösterilmiştir (16,88,97).

STAMP-2

STAMP-2 (six transmembran protein of prostate-2) ekspresyonunun PCa'larında fazla ekspresyonu olduğu bulunmuştur. STAMP-2'nin androjen reseptörü pozitif olan PCa hücrelerinde androjen ile düzenlendiği fakat androjen reseptörü negatif PCa hücrelerde ise ekpresyonunun olmadığı bulunmuştur (98).

KAYNAKLAR

1. Miller KD, Goding Sauer A, Ortiz AP, et al. Cancer statistics for hispanics/latinos, 2018. CA: a cancer journal for clinicians. 2018; 68(6), 425-445.
2. American Cancer Society (2019). American Cancer Society, Cancer Statistis Center 2019. (20/06/2019 date https://cancerstatisticscenter.cancer.org/#!/cancer-site/Prostate has been reached.)
3. Baade PD, Coory MD, Aitken JF et al. International trends in prostate-cancer mortality: the decrease is continuing and spreading. Cancer Causes & Control, 2004; 15(3), 237-241.
4. Cooperberg MR, Carroll PR, Klotz L. Active surveillance for prostate cancer: progress and promise. J Clin Oncol. 2011; 29 (27): 3669-76.
5. Draisma G, Etzioni R, Tsodikov A, et al. Lead time and overdiagnosis in prostate-specific antigen screening: Importance of methods and context. J Natl Cancer Inst. 2009; 101:374-383.
6. Jeldres C, Suardi N, Walz J, et al. Validation of the contemporary Epstein criteria for insignificant prostate cancer in Europeanmen. Eur Urol 2008; 54: 1306–13)
7. Walsh PC, Carmichael M, Brendler CB, et al. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. JAMA 1994;271:368–74
8. Lu-Yao GL, Albertsen PC, Moore DF, et al. Fifteen-year Outcomes Following Conservative Management Among Men Aged 65 Years or Older with Localized Prostate Cancer. Eur Urol 2015;68:805-811.
9. Epstein JI, Feng Z, Trock BJ, et al. Upgrading and downgrading of prostate cancer from biopsy to radical prostatectomy: incidence and predictive factors using the modified Gleason grading system and factoring in tertiary grades. Eur Urol 2012;61:1019-1024.
10. Epstein JI, Lotan TL. The Lower Urinary Tract and Male Genital System. In: Kumar V, Abbas AK, Fausto N, Aster JC, editors. Robbins and Cotran Pathologic Basis of Disease. 9th Ed. Philadelphia: Elsevier/Saunders; 2015. p. 959–90.

11. Humphrey PA, Moch H, Cubilla AL, et al. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs—Part B: Prostate and Bladder Tumours. Eur Urol. 2016;70(1):106-19.
12. McKenney JK. Prostate and Seminal Vesicles. In: Goldblum J, Lamps L, McKenney J, Myers J, editors. Rosai and Ackerman's Surgical Pathology. 11th Ed. Elsevier; 2018. p. 1097–134.
13. Bostwick D.G., Surgical pathology of the prostate, Chapter 32, in Modern Surgical Pathology, Ed: Widner N., Cote R.J., Suster S., Weiss L.M., Elsevier Science, Philadelphia, 1st ed, 2003: 1149-1196
14. Kumar V, Abbas AK, Fausto N, et al. (2014) Robbins and Cotran pathologic basis of disease, professional edition e-book. Elsevier health sciences.
15. De Marzo AM, DeWeese TL, Platz EA, et al. Pathological and molecular mechanisms of prostate carcinogenesis: implications for diagnosis, detection, prevention, and treatment. J cell Biochem 2004;91(3):459-77.
16. Konishi N, Shimada K, Ishida E, et al. Molecular pathology of prostate cancer. Pathol Int 2005;55(9):531-9.
17. Rubin, MA, De Marzo AM. Molecular genetics of human prostate cancer. Modern Pathology. 2004; 17(3), 380.
18. Ringer DP, Schnipper LE. Principles of Cancer Biology. İn: Lenhard RE, Osteen RT, Gansler T; eds. Clinical Oncology Atlanta: American Cancer Society, 2001; 21-35.
19. Benz C, Liu, E. T. (Eds.). (2012) Oncogenes and tumor suppressor genes in human malignancies (Vol. 63). Springer Science & Business Media.
20. Erol, A. Systemic DNA damage response and metabolic syndrome as a premalignant state. Current Molecular Medicine. 2010; 10(3), 321-334.
21. Hamilton JP. (2011). Epigenetics: principles and practice. Digestive diseases, 29(2), 130-135.
22. Kosova B, Özel TBR, Aktan TBÇ. Prostat kanseri tanısında DNA metilasyonunun yeri var mı?. Üroonkoloji Bülteni. 2011; 2, 33-40.
23. Jeronimo C, Henrique R. Epigenetic biomarkers in urological tumors: A systematic review. Cancer letters. 2014; 342(2), 264-274.
24. Lichtenstein P Holm NV, Verkasalo PK, et al. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med. 2000; 343(2):78–85.
25. Hjelmborg JB, Scheike T, Holst K, et al. The heritability of prostate cancer in the Nordic Twin Study of Cancer. Cancer Epidemiol Biomarkers Prev. 2014; 23(11):2303–10.
26. Verhage BA, Aben KK, Witjes JA, et al. Site-specific familial aggregation of prostate cancer. Int J Cancer. 2004; 109(4):611–7.
27. Mucci LA, Hjelmborg JB, Harris JR, et al. Familial Risk and Heritability of Cancer Among Twins in Nordic Countries. JAMA. 2016; 315(1):68–76.
28. Cooney KA, McCarthy JD, Lange E, et al. Prostate cancer susceptibility locus on chromosome 1q: a confirmatory study. J Natl Cancer Inst. 1997; 89(13):955–9.
29. Carter BS, Beaty TH, Steinberg GD, et al. Mendelian inheritance of familial prostate cancer. Proc Natl Acad Sci U S A. 1992; 89(8):3367–71.
30. Berry R, Schaid DJ, Smith JR, et al. Linkage analyses at the chromosome 1 loci 1q24-25 (HPC1), 1q42.2-43 (PCAP), and 1p36 (CAPB) in families with hereditary prostate cancer. Am J Hum Genet. 2000; 66(2):539–46.
31. Neuhausen SL, Farnham JM, Kort E, et al. Prostate cancer susceptibility locus HPC1 in Utah high-risk pedigrees. Hum Mol Genet. 1999; 8(13):2437– 42.

32. Xu J, Zheng SL, Chang B, et al. Linkage of prostate cancer susceptibility loci to chromosome 1. Hum Genet. 2001; 108(4):335–45.
33. Schleutker J, Matikainen M, Smith J, et al. A genetic epidemiological study of hereditary prostate cancer (HPC) in Finland: frequent HPCX linkage in families with late-onset disease. Clin Cancer Res. 2000; 6(12):4810–5.
34. Berry R, Schroeder JJ, French AJ, et al. Evidence for a prostate cancer-susceptibility locus on chromosome 20. Am J Hum Genet. 2000; 67(1):82–91.
35. Breyer JP, Avritt TG, McReynolds KM, et al. Confirmation of the HOXB13 G84E germline mutation in familial prostate cancer. Cancer Epidemiol Biomarkers Prev. 2012; 21(8):1348–53.
36. Xu J, Lange EM, Lu L, et al. HOXB13 is a susceptibility gene for prostate cancer: results from the International Consortium for Prostate Cancer Genetics (ICPCG). Hum Genet. 2013; 132(1):5–14.
37. Ledet EM, Sartor O, Rayford W, et al. Suggestive evidence of linkage identified at chromosomes 12q24 and 2p16 in African American prostate cancer families from Louisiana. Prostate. 2012; 72(9):938–47.
38. Brown WM, Lange EM, Chen H, et al. Hereditary prostate cancer in African American families: linkage analysis using markers that map to five candidate susceptibility loci. Br J Cancer. 2004; 90(2):510–4.
39. Matsui H, Suzuki K, Ohtake N, et al. Genomewide linkage analysis of familial prostate cancer in the Japanese population. J Hum Genet. 2004; 49(1):9–15.
40. Baffoe-Bonnie AB, Kittles RA, Gillanders E, et al. Genomewide linkage of 77 families from the African American Hereditary Prostate Cancer study (AAHPC). Prostate. 2007; 67(1):22–31.
41. Cheng HH, Pritchard CC, Boyd T, et al. Biallelic inactivation of BRCA2 in platinum-sensitive metastatic castration-resistant prostate cancer. European urology. 2016; 69(6), 992-995.
42. Castro E, Goh C, Olmos D, et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. Journal of Clinical Oncology. 2013; 31(14), 1748.
43. Eeles RA, Kote-Jarai Z, Al Olama AA, et al. Identification of seven new prostate cancer susceptibility loci through a genome-wide association study. Nature genetics. 2009; 41(10), 1116.
44. Yeager M, Orr N, Hayes RB, et al. Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. Nat Genet. 2007; 39(5):645–9.
45. Falzarano SM, Zhou M, Carver P, et al. ERG gene rearrangement status in prostate cancer detected by immunohistochemistry. Virchows Arch 2011;459(4):441-7.
46. King JC, Xu J, Wongvipat J, et al. Cooperativity of TMPRSS2-ERG with PI3-kinase pathway activation in prostate oncogenesis. Nature genetics. 2009; 41(5), 524.
47. Tomlins SA, Day JR, Lonigro RJ, et al. Urine TMPRSS2: ERG plus PCA3 for individualized prostate cancer risk assessment. European urology. 2016; 70(1), 45-53.
48. Korkolopoulou P, Levidou G, Trigka EA, et al. A comprehensive immunohistochemical and molecular approach to the PI3K/AKT/mTOR (phosphoinositide 3-kinase/v-akt murine thymoma viral oncogene/mammalian target of rapamycin) pathway in bladder urothelial carcinoma. BJU Int. 2012; 110(11 Pt C): p. E1237-48.).
49. Vivanco I, Sawyers CL. The phosphatidylinositol 3-Kinase AKT pathway in human cancer. Nat Rev Cancer. 2002; 2(7): p. 489-501.

50. Guertin DA, Sabatini DM. Defining the role of mTOR in cancer, Cancer Cell. 2007; 12(1): p. 9-22.].
51. Samuels Y, Wang Z, Bardelli A, et al. High frequency of mutations of the PIK3CA gene in human cancers. Science. 2004; 304(5670), 554-554.
52. Zhou X, Tan M, Stone Hawthorne V, et al. Activation of the Akt/mammalian target of rapamycin/4E-BP1 pathway by ErbB2 overexpression predicts tumor progression in breast cancers. Clin Cancer Res. 2004; 10(20): p. 6779-88.
53. Lang SA, Gaumann A, Koehl GE, et al. Mammalian target of rapamycin is activated in human gastric cancer and serves as a target for therapy in an experimental model. Int J Cancer. 2007; 120(8): p. 1803-10.
54. Nozawa H, Watanabe T, Nagawa H. Phosphorylation of ribosomal p70 S6 kinase and rapamycin sensitivity in human colorectal cancer. Cancer Lett. 2007; 251(1): p. 105-13.
55. Sun H, Lesche R, Li DM, et al. PTEN modulates cell cycle progression and cell survival by regulating phosphatidylinositol 3,4,5-trisphosphate and Akt/protein kinase B signaling pathway. Proc Natl Acad Sci USA. 1999; 96: 6199–204.
56. Wang S, Parsons R, Ittmann M. Homozygous deletion of the PTEN tumor suppressor gene in a subset of prostate adenocarcinomas. Clin Cancer Res 1998;4(3):811-5. 68
57. Schrecengost R, Knudsen KE, Molecular pathogenesis and progression of prostate cancer. Semin Oncol. 2013; 40(3): p. 244-58.
58. Jamaspishvili T, Berman DM, Ross AE, et al. Clinical implications of PTEN loss in prostate cancer. Nature Reviews Urology, 2018; 15(4), 222.
59. Weinmaster GERRY, Roberts VJ, Lemke G. A homolog of Drosophila Notch expressed during mammalian development. Development. 1991; 113(1), 199-205.
60. Artavanis-Tsakonas S, Matsuno K, Fortini ME. Notch signaling. Science. 1995; 268(5208), 225-232.
61. Sahlgren C, Gustafsson MV, Jin S, et al. Notch signaling mediates hypoxia-induced tumor cell migration and invasion. Proceedings of the National Academy of Sciences. 2008; 105(17), 6392-6397.
62. Kidd S, Kelley MR, Young MW. Sequence of the notch locus of Drosophila melanogaster: relationship of the encoded protein to mammalian clotting and growth factors. Molecular and cellular biology. 1986; 6(9), 3094-3108.
63. Ohishi K, Varnum-Finney B, Flowers D, et al. Monocytes express high amounts of Notch and undergo cytokine specific apoptosis following interaction with the Notch ligand, Delta-1. Blood. 2000; 95(9), 2847-2854.).
64. Ellisen LW, Bird J, West DC, et al. TAN-1, the human homolog of the Drosophila notch gene, is broken by chromosomal translocations in T lymphoblastic neoplasms. Cell. 1991; 66(4), 649-661.
65. Pear WS, Aster JC, Scott ML, et al. Exclusive development of T cell neoplasms in mice transplanted with bone marrow expressing activated Notch alleles. Journal of Experimental Medicine. 1996; 183(5), 2283-2291.
66. Oda T, Elkahloun AG, Pike BL, et al. Mutations in the human Jagged1 gene are responsible for Alagille syndrome. Nature genetics. 1997; 16(3), 235.
67. Grishina IB, Kim SY, Ferrara C, et al. BMP7 inhibits branching morphogenesis in the prostate gland and interferes with Notch signaling. Developmental biology. 2005; 288(2), 334-347.

68. Wang Z, Banerjee S, Li Y, et al. Down-regulation of Notch-1 inhibits invasion by inactivation of nuclear factor-κB, vascular endothelial growth factor, and matrix metalloproteinase-9 in pancreatic cancer cells. Cancer research. 2006; 66(5), 2778-2784.
69. Wang J, Shelly L, Miele L, et al. Human Notch-1 inhibits NF-κB activity in the nucleus through a direct interaction involving a novel domain. The Journal of Immunology. 2001;167(1), 289-295.
70. Garcia A, Kandel JJ. Notch: a key regulator of tumor angiogenesis and metastasis. Histology and histopathology. 2012; 27(2), 151.
71. Zhu H, Zhou X, Redfield S, et al. Elevated Jagged-1 and Notch-1 expression in high grade and metastatic prostate cancers. American journal of translational research. 2013; 5(3), 368.
72. Santagata S, Demichelis F, Riva A,et al. JAGGED1 expression is associated with prostate cancer metastasis and recurrence. Cancer research. 2004; 64(19), 6854-6857.
73. Hafeez BB, Adhami VM, Asim M, et al. Targeted knockdown of Notch1 inhibits invasion of human prostate cancer cells concomitant with inhibition of matrix metalloproteinase-9 and urokinase plasminogen activator. Clinical cancer research. 2009; 15(2), 452-459.
74. Cooper CR, Chay CH, Gendernalik JD, et al. Stromal factors involved in prostate carcinoma metastasis to bone. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2003; 97(S3), 739-747.
75. Swanson GP, Thompson IM, Basler J. Current status of lymph node-positive prostate cancer: incidence and predictors of outcome. Cancer. 2006; 107(3), 439-450.
76. Salvati M, Frati A, Russo N, et al. Brain metastasis from prostate cancer. Report of 13 cases and critical analysis of the literature. Prostate. 2005; 2, 10.
77. Shou J, Ross S, Koeppen H, et al. Dynamics of notch expression during murine prostate development and tumorigenesis. Cancer research. 2001; 61(19), 7291-7297.
78. Zayzafoon M, Abdulkadir SA, McDonald JM. Notch signaling and ERK activation are important for the osteomimetic properties of prostate cancer bone metastatic cell lines. Journal of Biological Chemistry. 2004; 279(5), 3662-3670.
79. Bastian PJ, Yegnasubramanian S, Palapattu GS, et al. Molecular biomarker in prostate cancer: the role of CpG island hypermethylation. Eur Urol 2004;46(6):698-708.
80. Nelson WG, Yegnasubramanian S, Agoston AT, et al. Abnormal DNA methylation, epigenetics, and prostate cancer. Front Biosci. 2007;12:4254-66.
81. Gurel B, Iwata T, Koh CM, et al. Molecular alterations in prostate cancer as diagnostic, prognostic, and therapeutic targets. Adv Anat Pathol. 2008; 15(6):319-31.)
82. Yegnasubramanian S, Kowalski J, Gonzalgo ML, et al. Hypermethylation of CpG islands in primary and metastatic human prostate cancer. Cancer Res 2004;64(6):1975-86.
83. He WW, Sciavolino PJ, Wing J, et al. A novel human prostate-specific, androgen-regulated homeobox gene (NKX3.1) that maps to 8p21, a region frequently deleted in prostate cancer. Genomics. 1997;43(1):69-77).
84. Cote RJ, Shi Y, Groshen S, Feng AC, et al. Association of p27 Kip1 levels with recurrence and survival in patients with stage C prostate carcinoma. J Natl Cancer Inst. 1998;90(12):916-20.
85. Guo Y, Sklar GN, Borkowski A, et al. Loss of the cyclin-dependent kinase inhibitor p27(Kip1) protein in human prostate cancer correlates with tumor grade. Clin Cancer

Res. 1997;12(1):2269-74.).
86. Hughes C, Murphy A, Martin C, et al. Molecular pathology of prostate cancer. J Clin Pathol. 2005;58(7):673-84.
87. Konishi N, Hiasa Y, Tsuzuki T, et al. Detection of pRB, p16/CDKN2 and p15INK4B gene alterations with immunohistochemical studies in human prostate carcinomas. Int J Oncol. 1996;8(1):107-12.
88. Evangelos M, Alexios T. Molecular pathways in prostate cancer Nephro-Urology Monthly. 2013;5(3):792-800.
89. Rodrigues DN, Butler LM, Estelles DL, et al. Molecular pathology and prostate cancer therapeutics: from biology to bedside. J Pathol 2014;232(2):178-84.
90. Zegarra-Moro OL, Schmidt LJ, Huang H, et al. Disruption of androgen receptor function inhibits proliferation of androgen-refractory prostate cancer cells. Cancer Res. 2002;62;1008–13.).
91. Reiter RE, Gu Z, Watabe T, et al. Prostate stem cell antigen: a cell surface marker overexpressed in prostate cancer. Proc Natl Acad Sci USA. 1998;95(4):1735-40.).
92. Gu Z, Thomas G, Yamashiro J, et al. Prostate stem cell antigen (PSCA) expression increases with high gleason score, advanced stage and bone metastasis in prostate cancer. Oncogene. 2000;19(10):1288-96.).
93. Sato K, Qian J, Sezak JM, et al. Clinical significance of alterations of chromosome 8 in high-grade, advanced, nonmetastatic prostate carcinoma. J Natl Cancer Inst. 1999;91(18):1574-80.).
94. Downward, J. Targeting RAS signalling pathways in cancer therapy. Nature Reviews Cancer. 2003; 3(1), 11.
95. Koh CM, Bieberich CJ, Dang CV, et al. MYC and prostate cancer. Genes & cancer. 2010; 1(6), 617-628.
96. Hobbs GA, Der CJ, Rossman KL. RAS isoforms and mutations in cancer at a glance. J Cell Sci. 2016; 129(7), 1287-1292.
97. Bubendorf L, Kononen J, Koivisto P, et al. Survey of gene amplifications during prostate cancer progression by highthroughout fluorescence in situ hybridization on tissue microarrays. Cancer Res. 1999;59(4):803-6.).
98. Jin Y, Wang L, Qu S, et al. STAMP2 increases oxidative stress and is critical for prostate cancer. EMBO molecular medicine. 2015; 7(3), 315-331.