Aberrant Expression of Forkhead Box Proteins in Prostate Cancer Development

Forkhead Box Proteinlerinin Prostat Kanser Gelişiminde Değişmiş İfadeleri

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ABSTRACT

Prostate cancer is one of the most common types of cancer in men. The evolutionarily-conserved Forkhead-box (FOX) family proteins are able to bind to promoters and enhancers in a sequence-specific way to regulate gene expression. FOX proteins participate in the most diverse range of biological functions from genetic diseases to cancers. Recent studies over the past few years demonstrated the dysregularity of the FOX family proteins which lead to prostate cancer pathogenesis and their role as an oncogene or tumor suppressor in prostate cancer. In addition, experimental studies have shown that the dysregulation of FOX proteins is associated with cancer initiation, proliferation, migration, invasion, metastasis and survival. In this review, we summarized the roles of FOX proteins in the pathogenesis of prostate cancer and evaluated their potential as targets for therapeutic intervention.

Key Words: Forkhead box protein, oncogene, tumor suppressor, prostate cancer

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ÖZET

Prostat kanseri erkeklerde en sık görülen kanser türlerinden biridir. Evrimsel olarak korunmuş olan Forkhead-box (FOX) ailesi proteinleri, gen ekspresyonunu düzenlemek için promotörler ve güçlendiriciler üzerine dizile özgü bir şekilde bağlanabilir. FOX proteinleri genetik hastalıklardan kanserlere kadar çok çeşitli biyolojik fonksiyonlara katılır. Son birkaç yıldaki çalışmalar, prostat kanserine yol açan FOX ailesi proteinlerinin düzenliliğini ve onların prostat kanserinde onkogen veya tümör baskılayıcı rollerini göstermiştir. Ayrıca, deneySEL çalışmalar FOX proteinlerinin düzenliliğini kanser başlatma, proliferasyon, migrasyon, invazyon, metastaz ve sağkalım ile ilişkili olduğunu göstermiştir. Bu derlemede, prostat kanseri patogenezinde FOX proteinlerinin rollerini özetleyerek, terapötik müdahale hedefleri olarak potansiyellerini değerlendirdik.

Anahtar Sözcükler: Forkhead box protein, onkogen, tümör supresör, prostat kanser

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FOXA in the Biology of Prostate Cancer

FOXA1, FOXA2 and FOXA3, also known as hepatocyte nuclear factor 3 (HNF3) α, HNF3β and HNF3y respectively, are members of the FOX subfamily and play important roles in the development and maintenance of the endoderm-derived organs and regulation of gene transcription. FOXA proteins can interact with chromatin and directly modulate the chromatin structure, thereby facilitating the binding of other transcription factors to DNA. Therefore, they function as a pioneer transcription factor (4). Moreover, it has been reported that FOXA1 participates in androgen receptor (AR)-mediated gene regulation in prostate cancer. Two independent groups of scholars reported similar findings for how FOXA1 controls the AR cistrome in prostate cancer (5, 6). In both studies, the FOXA1 gene was silenced by siRNA in prostate cancer cell lines and then AR ChIP-seq was performed. Depending on the loss of FOXA1, loss of about 50% AR-binding events was observed while the remaining 50% of AR-binding events still existed independent of FOXA1. Interestingly, as many as three times more new AR-binding events have occurred while FOXA1 was absent. Hence, it has been suggested that FOXA1 has a dual role in prostate cancer as it can both mediate AR-binding events and prevent additional AR-binding events by simultaneously altered AR to cognate androgen response elements and normalizing the androgen signal in Drosophila melanogaster (3). Since then, fifty different FOX proteins identified in humans have been divided into 19 subfamilies (FOXA to FOXS) based on their protein sequence homology (2). It has been shown that FOX proteins family play important roles in a wide variety of biological processes, such as cell proliferation, differentiation, migration, invasion, survival, apoptosis and DNA damage repair. FOX proteins family is expressed differentially in prostate cancer. For this reason, dysregulation of some FOX proteins contribute to the pathogenesis of the cancer.

In this review, we aim to explain the roles played by FOX proteins in the pathogenesis of prostate cancer. We mainly focused on the relationship between prostate cancer and the FOX subfamilies (FOXA, FOXM, FOXO and FOXP) that were identified in humans have been divided into 19 subfamilies (FOXA to FOXS) based on their protein sequence homology (2). It has been shown that FOX proteins family play important roles in a wide variety of biological processes, such as cell proliferation, differentiation, migration, invasion, survival, apoptosis and DNA damage repair. FOX proteins family is expressed differentially in prostate cancer. For this reason, dysregulation of some FOX proteins contribute to the pathogenesis of the cancer.

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In addition, Zhang et al. have demonstrated that treatment with methlyselenic acid (MSA) caused the increase of FOXO1 expression in prostate cancer cells (36). Another study tested the effects of statins on cell proliferation and apoptosis on human prostate cancer cell lines. In this study, it was observed that AKT/FOXO1 phosphorylation was downregulated in prostate cancer cells. Furthermore, statins decreased cell proliferation and induced apoptosis in prostate cancer cells in a dose- and time-dependent manner (37).

FOXO in the Biology of Prostate Cancer

For knock box P (FOXp) subfamily members consist of FOXP1, FOXP2, FOXP3 and FOXP4 in vertebrates. The studies investigating the roles played by the members of this subfamily in prostate cancer have revealed that each FOXP transcription factor possesses a different role in prostate cancer. It has been put forward that FOXP1, FOXP3 and FOXP4 act as tumor suppressors, whereas FOXP2 acts as an oncogene in prostate cancer (38-42).

In a study conducted by Banham et al., FOXP1 was frequently overexpressed in both nuclear and cytoplasmic compartments in prostate tumors compared to their normal counterparts (38). A tissue microarray study made on 11,000 normal prostate epithelium and cancerous tissues demonstrated that FOXP2 upregulation was associated with poor prognosis in ERG-negative prostate cancer (40). In contrast to oncogenic role of FOXP2, Takayama et al. have reported that FOXP1 acted as a tumor suppressor through inhibiting cell proliferation and migration in prostate cancer. In this study, decreased expression of FOXP1 in prostate cancer tissue samples were associated with poor prognosis and had a prognostic value in prostate cancer (41). Single nucleotide polymorphisms (SNPs) in FOXP3 (rs3761548) and FOXP4 (rs1983891) genes may have an association with susceptibility to prostate cancer (42, 43). Furthermore, a systematic meta-analysis from at least three independent population-based case-control studies performed by Hao et al. have explained that 20 genetic variants in 19 different genes, including FOXP4, had significant association with prostate cancer risk (44). Furthermore, it has been reported that FOXP proteins interact with a variety of signaling pathways and different molecules. It has been shown that miR-16a/b induced by FOXP3 inhibited tumor-suppressive activity during tumor initiation in prostate cancer (45). Song et al. have shown that overexpression of miR-618 inhibits prostate cancer migration and invasion through the FOXP2 gene (46). Hirayonmus et al. have shown that deletion of both FOXP1–SHQ1 and PTEN were correlated with prostate oncogenesis (47). Wang et al. have demonstrated that c-MYC transcription, which was frequently upregulated in prostate cancer, was repressed by FOXP3 in prostate cells. They have also reported that FOXP3 played a suppressive role in prostate cancer development by modulating the expression of c-MYC (39). Lastly, in a recent study conducted by Wu et al. it has been reported that loss of FOXP3 and TSC1 promoted prostate cancer progression via transcriptional and post-translational regulation of c-MYC (48).

Other Important FOX Transcription Factors in Prostate Cancer

In addition to the FOX proteins mentioned above, there are several other FOX proteins that have been reported to play a role in prostate cancer. However, since there are not a sufficient number of studies about these proteins, we have not covered them in detail in this review. For instance, it has been reported that FOXC1, FOXC2, FOXJ2 and FOXJ1 were upregulated in prostate cancer tissues and cell lines (49-52). In addition, the studies about FOXJ1 expression as a potential cause of prostate cancer put forward controversial results. While some studies assert that FOXJ1 is highly expressed in prostate cancer tissues, another study showed that FOXJ1 was downregulated in prostate cancer tissues (53, 54). Zhang et al. postulated that FOXJ3 was the downstream target of miR-425-5p and high miR-425-5p expression was associated with prostate cancer development via FOXJ3 (55).

CONCLUSION

Evidence from experimental and clinical studies indicate that aberrant expressions of FOX family transcription factors promote the progression of prostate cancer. Furthermore, FOX family transcription factors can act both as an oncogene and as a tumor suppressor in prostate cancer. 50 FOX transcription factors have been identified in humans, but the role of many in prostate cancer still remains unknown. Hence, precise mechanisms through which FOX proteins affect prostate cancer and the unexplained roles of many FOX proteins in prostate cancer need to be investigated further in the future.
In addition, recent studies demonstrate that miRNAs are involved in the regulation of FOX proteins in prostate cancer. Therefore, comprehensive investigation of FOX-related miRNAs appears to be promising to provide novel therapeutic strategies for prostate cancer in the future. Lastly, the identification of small molecules that selectively block the functioning of FOX proteins and their adoption with siRNAs for suppressing the expression of FOX proteins can help increase the effectiveness of prostate cancer treatment.

Conflict of interest
No conflict of interest was declared by the authors.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394-424.

2. Lam EW, Gomes AR. Forkhead box transcription factors in cancer initiation, progression and chemotherapeutic drug response. Front Oncol 2014; 4: 305.

3. Weigel D, Jürgens G, Küttner F, Seifert E, Jäckle H. The homeotic gene fork head encodes a nuclear protein and is expressed in the terminalregions of the Drosophila embryo. Cell 1989; 57: 645-58.

4. Jozwik KM, Carroll JS. Pioneering factors in hormone-dependent cancers. Nat Rev Cancer 2012; 12(6): 381-5.

5. Wang D, Garcia-Bassets I, Benner C, Li W, Su X, Zhou Y, et al. Reprogramming of transcription by distinct classes of enhancers functionally defined by eRNA. Nature 2011; 474: 390-4.

6. Sahu B, Laakso M, Ovaska K, Mirtti T, LIndn J, Rannikko A, et al. Dual role of FoxA1 in androgen receptor binding to chromatin, androgen signalling and prostate cancer. EMBO J 2011; 30: 3962–76.

7. Jin HJ, Zhao JC, Wu L, Kim J, Yu, J. Cooperativity and equilibrium with FOXA1 define the androgen receptor transcriptional program. Nat Commun 2014: 5: 3972.

8. Jin HJ, Zhao JC, Ogden I, Bergan RC, Yu J. Androgen receptor-independent function of FoxA1 in prostate cancer metastasis. Cancer Res 2013; 73: 3725–3732.

9. Jain RK, Mehta RJ, Nakshatri H, Idreess MT, Badve SS. High-level expression of forkhead-box protein A1 in metastatic prostate cancer. Histopathology 2011; 58: 766-72.

10. Park JW, Lee JK, Witte ON, Huang J. FOXA2 is a sensitive and specific marker for small cell neuroendocrine carcinoma of the prostate. Mod Pathol 2017; 30: 1262-72.

11. Mirosevich J, Gao N, Gupta A, Shappell SB, Jove R, Matusik RJ. Expression and role of FoxA proteins in prostate cancer. Prostate 2006; 66: 1013-28.

12. Albayrak G, Konac E, Uguras Dikmen A, Bilen CY. FOXA1 knock-out via CRISPR/Cas9 altered Casp-9, Bax, CCND1, CDK4, and fibronectin expressions in LNCaP cells. Exp Biol Med 2018; 243: 990-4.

13. Barbieri CE, Baca SC, Lawrence MS, Demichielis F, Blattner M, Theurillat JP, et al. Exome sequencing identifies recurrent SPOP, FOXA1 and MED12 mutations in prostate cancer. Nat Genet 2012; 44: 685-9.

14. Grasso CS, Wu YM, Robinson DR, Cao X, Dhanasekaran SM, Khan AP, et al. The mutational landscape of lethal castration-resistant prostate cancer. Nature 2019; 571: 413-8.

15. Kalin TV, Wang IC, Ackerson TJ, Major ML, Detrisac CJ, Kalinichenko VV, et al. Increased levels of the FoxM1 transcription factor accelerate development and progression of prostate carcinomas in both TRAMP and LADY transgenic mice. Cancer Res 2006; 66: 1712-20.

16. Chandran UR, Dhir MR, Bisceglia M, Lyons-Weiler M, Liang W, Michalopoulos G, et al. Gene expression profiles of prostate cancer reveal involvement of multiple molecular pathways in the metastatic process. BMC Cancer 2007; 7: 64.

17. Ananna M, Vaavitsainen S, Vandekerkhove G, Bacon JWW, Beja K, Chi KN, et al. Frequent mutation of the FOXA1 untranslated region in prostate cancer. Commun Biol 2018; 1: 122.

18. Wedge DC, Gendum G, Mitchell T, Woodcock DJ, Martincorena I, Ghori M, et al. Sequencing of prostate cancers identifies new cancer genes, routes of progression and drug targets. Nat Genet 2018; 50: 682-92.

19. Zhao X, Lei Y, Li G, Cheng Y, Yang H, Xie L, et al. Integrative analysis of cancer driver genes in prostate adenocarcinoma. Mol Med Rep 2019; 19: 2707-15.

20. Adams EJ, Karthaus WR, Hoover E, Liu D, Gruet A, Zhang Z, et al. FOXA1 mutations alter pioneering activity, differentiation and prostate cancer phenotypes. Nature 2019; 571: 408-12.

21. Parolai A, Cieslik M, Chu SC, Xiao L, Ouchi T, Zhang Y, et al. Distinct structural classes of activating FOXA1 alterations in advanced prostate cancer. Nature 2019; 571: 413-8.
40. Stumm L, Burkhardt L, Steurer S, Simon R, Adam M, Becker A, et al. Strong expression of the neuronal transcription factor FOXP2 is linked to an increased risk of early PSA recurrence in ERG fusion-negative cancers. J Clin Pathol 2013; 66: 563-8.

41. Takayama KI., Suzuki T, Tsutsumi S, Fujimura T, Takahashi S, Homma Y, et al. Integrative analysis of FOXP1 function reveals a tumor-suppressive effect in prostate cancer. Mol Endocrinol 2014; 28: 2012-24.

42. Liu M, Shi X, Wang J, Xu Y, Wei D, Zhang Y, et al. Association of FOXP4 Gene with Prostate Cancer and the Cumulative Effects of rs4714476 and 8q24 in Chinese Men. Clin Lab 2015; 61: 1491-9.

43. Chatrabnous N, Ghaderi A, Ariafar A, Razeghinia MS, Nemati M, Jafarzadeh A. Serum concentration of interleukin-35 and its association with tumor stages and FOXP3 gene polymorphism in patients with prostate cancer. Cytokine 2019; 113: 221-7.

44. Hao Q, Wei D, Zhang Y, Chen X, Yang F, Yang Z, et al. Systematic meta-analyses of gene-specific genetic association studies in prostate cancer. Oncotarget 2016; 7: 22271-84.

45. Liu R, Yi B, Wei S, Yang WH, Hart KM, Chauhan P, et al. FOXP3–miR-146–NF-κB Axis and Therapy for Precancerous Lesions in Prostate. Cancer Res 2015; 75: 1714-24.

46. Song XJ, Tang Y, Lei XH, Zhao ZQ, Wu ZQ. miR-618 inhibits prostate cancer migration and invasion by targeting FOXP2. J Cancer 2017; 8: 2501-10.

47. Hieronymus H, Iaquinta PJ, Wongvipat J, Gopalan A, Murali R, Mao N, et al. Deletion of 3p13-14 locus spanning FOXP1 to SHQ1 cooperates with PTEN loss in prostate oncogenesis. Nat Commun 2017; 8: 1081.

48. Wu L, Yi B, Wei S, Rao D, He Y, Naik G, et al. Loss of FOXP3 and TSC1 Accelerates Prostate Cancer Progression through Synergistic Transcriptional and Posttranslational Regulation of c-MYC. Cancer Res 2019; 79: 1413-25.

49. Peraldo-Neia C, Migliardi G, Mello-Grand M, Montermino F, Segir R, Pignochino Y., et al. Epidermal Growth Factor Receptor (EGFR) mutation analysis, gene expression profiling and EGFR protein expression in primary prostate cancer. BMC Cancer 2011; 11: 31.

50. Báretzén A, Gravdal K, Haukaas SA, Beisland C, Akslen LA, Halvorsen OI. FOXC2 expression and epithelial-mesenchymal phenotypes are associated with castration resistance, metastasis and survival in prostate cancer. J Pathol Clin Res 2019; 5: 272-286.

51. Nikitina AS, Sharova EI, Danilenko SA, Butusova TB, Vasiliev AO, Govorov AV, et al. Novel RNA biomarkers of prostate cancer revealed by RNA-seq analysis of formalin-fixed samples obtained from Russian patients. Oncotarget 2017; 8: 32990-3001.

52. Zhang X, Wang L, Wang Y, Shi S, Zhu H, Xiao F, et al. Inhibition of FOXQ1 induces apoptosis and suppresses proliferation in prostate cancer cells by controlling BCL11A/MDM2 expression. Oncol Rep 2016; 36: 2349-56.

53. Lan Y, Hu X, Jiang K, Yuan W, Zheng F, Chen H. Significance of the detection of TIM-3 and FOXJ1 in prostate cancer. J BUON 2017; 22:1017-1021.

54. An Q, Liu D, Zou L. The expression and functional role of FOX transcription factor FOXJ1 in prostate cancer. Int J Clin Exp Med 2017; 10: 285-92.

55. Zhang JY, Su XP, Li YN, Guo YH. MicroRNA-425-5p promotes the development of prostate cancer via targeting forkhead box J3. Eur Rev Med Pharmacol Sci 2019; 23: 547-54.