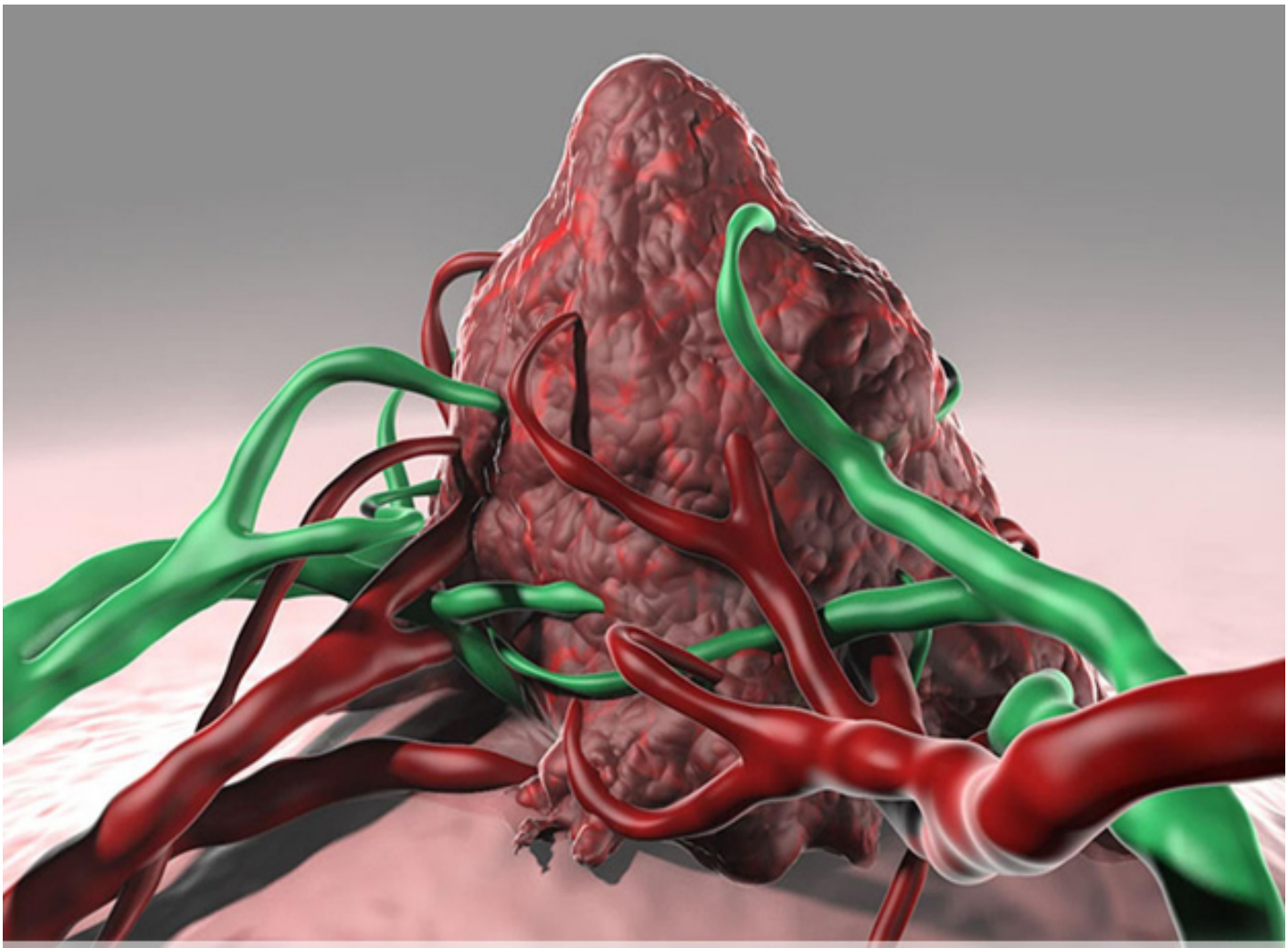

CANCER THERAPY

ISBN 978-81-936678-8-0

MEDDOCS
Open Access Publisher

Molecular drug resistance mechanisms in Prostate Cancer

Corresponding Author: Sercan ERGÜN

Department of Medical Biology, Faculty of Medicine, Ordu University, 52200, Altınordu, Ordu, TURKEY

ORCID: 0000-0002-6733-984

Email: sercanergun@msn.com

Published Online: Jan 24, 2019

eBook: Cancer Therapy

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Introduction

Cancer cells are equipped for adjustment prompting drug resistance, which is the fundamental issue of treatment in all malignant growths, like Prostate Cancer (PC). Despite the fact that a wide scope of anticancer drugs, including research-based agents and medications confirmed for human use, is accessible, most of them lose their treatment efficiency in course of time [1]. The androgen-dependent pathway is yet a primary focus in PC, which is the second in occurrence and the first in mortality among cancer types in all over the world [2]. The Androgen Receptor (AR) is a main component of the pathway. Inert AR is generally found in the cytoplasm. When a ligand (dihydrotestosterone, DHT or testosterone) is bound to it, AR is moved into the nucleus and functions as a Transcription Factor (TF) to trigger expression of many genes in charge of modulating cell differentiation and proliferation. In most of cases, PC is sensitive to the blood testosterone concentration on early treatment. In this way, decreasing androgen accessibility represses or suspends the disease progression. In any case, drug resistance definitely advances in course of time, prompting a fast PC progression in androgen deficiency [1]. Various new medications have newly taken part in clinical usage to treat PC (also metastatic PC) advancing at constrained androgen accessibility. Anti-androgen medications, for example, enzalutamide and abiraterone, balance out the disease progression and suspend the beginning of chemotherapy [3,4]. However, the tumor turns into insensitive to the medications with time and, in addition, generates cross-resistance; in another saying, resistance to one medication produces a weak efficiency of following therapy with different medications [5]. Tumors resistant to anti-androgens are major downsides of recent uro-oncology. This chapter includes different pathways responsible for drug resistance in PC. The pathways may classically be separated into two massive sets as androgen-dependent and androgen-independent. The drug resistance mechanisms contains increased transcriptional activity of AR; AR mutations affecting binding efficiencies of AR ligands; expression of abnormally expressed functional AR splice variants, that don't need a ligand for activation; over-expression of genes associated with androgenic hormone synthesis; and lots of alternative mechanisms [6].

Increased transcriptional efficiency of AR

Numerous investigations have appeared that post-translational AR alterations may upgrade transcriptional efficiency AR at reduced androgen levels. This can conduce to AR re-activation within CRPC status, and improvement of insensitivity to CYP17A1 blockers like abiraterone [7]. Tyrosine phosphorylation of AR is frequently seen in hormone-insensitive when compared to sensitive cases, and findings propose that phosphorylation controls AR transcriptional efficiency [8]. Tyrosine phosphorylation is modulated by proteins like SRC and ACK1, which are

up-regulated when androgen concentrations are decreased. Co-activator proteins' increased transcriptional activity, or co-repressor proteins' decreased efficiency, may thence increment AR transcriptional efficiency, and can be crucial in progressive PC development during androgen deprivation and insensitivity to CYP17A1 blockers. In the androgen depletion, AR activation can be activated by interleukin 6 (IL-6) and Src-1 [9]. Rised activity of SRC1 in non-metastasized PC is correlated with a more aggressive characteristic, and reduced expression depresses PC development and AR transcriptional efficiency [10]. Up-regulation of IL-6 takes a crucial function in PC development and the formation of CRPC. IL-6 can trigger insensitivity to anti-androgens by overexpression of Translation Initiation Factor eIF4A (TIF2). An identical system of insensitivity can originate for enzalutamide. Increased levels of TIF2 at androgen deficient media can trigger increased AR efficiency in case of ligand absence [11].

In a huge Phase III clinical trial, READY, evaluating dasatinib, which is a multi-kinase blocker and known to suppress SRC in a combinatorial manner together with docetaxel in patients with chemotherapy-naive CRPC, there was not a difference observed in median OS between docetaxel alone *versus* dasatinib plus docetaxel, unfortunately [39]. Furthermore, a chimeric monoclonal antibody against IL-6, siltuximab (CNTO 328), has composed encouraging outcomes in a Phase I clinical trial in a combinatorial manner together with docetaxel; yet, two following Phase II clinical trials of siltuximab (applied as alone or in a combinatorial manner together with mitoxantrone) presented minimum clinical efficiency in CRPC [12,13].

AR conformational changes for alternate activation systems

Among the systems implemented by cancer cells to overcome apoptosis initiation by Androgen Deprivation Therapy (ADT), a few systems include useful adjustments of AR activities. One of the preceding findings in figuring out the advancement of hormone-resistant disease accompanied with the detection of AR gene overexpression [14], observed in approximately one fourth of Castration Resistant Prostate Cancer (CRPC) tissue samples however actually not expressed in hormone-sensitive tumor [15]. Also, researches have demonstrated that anti-androgen resistance is coherently associated with over-expression of AR, projecting adjustments to enhance responsiveness to fallen androgen (ligand) levels in continuing AR programs [16]. Anti-androgens utilized in combinatorial androgen stoppage in hormone-responsive disease generally use bicalutamide, and less frequently nilutamide and flutamide. A critical perception in this setting was that 15-30%. A crucial investigation in this program was that 15-30% of tumoral tissues, after getting insensitive to androgen stoppage, would display relapses after stopping of treatment, an event clinically described as anti-Androgen Withdrawal Syndrome (AWS) [17]. Presently, it is welcomed that specific AR mutations are admitted to cause reactivation of AR signaling; T877A mutation, for instance, gives insensitivity against hydroxyflutamide, the effective structure of flutamide [18]. A different mutation of AR ligand binding area, W741C/L, provides insensitivity against bicalutamide [19]. Furthermore, the formerly referenced T877A mutation accompanied with a different AR mutation L701H practically presents a complicated glucocorticoid-based activation of AR [20]. When AR-dependent target genes in androgen-dependent and androgen-independent cells are compared, it is shown that AR-modulated transcriptional system is prominently changed in castration-insensitive disease, particularly with regards to cell cycle related genes, causing the cell cycle checkpoints' inactivation [21].

Splice variants of androgen receptor

Over-expression of constitutively functional AR splice variants (AR-Vs) shows a crucial molecular mechanism for tumor development in the course of ADT, and seems to be a significant clinical mechanism of insensitivity to AR-targeted drugs in patients with mCRPC [22]. Numerous alternately spliced AR-Vs are deprived of ligand-binding domain at C-terminal however keep the trans-activating domain at N-terminal, driving to constitutively functional AR in a ligand-independent manner [23]. Truncated patterns of full-length AR (AR-V11 to AR-V1) or skipped/missing exons (AR-V12 to AR-V14 and AR-V567es) are ways to form AR-Vs [22]. Among the distinct AR alternatives described in PC, ARv567es and AR-V7 are the most prevalent [24]. Both are over-expressed in mCRPC when compared to hormone-naive metastatic cancer, although V7 has only been constitutively expressed in human specimens. AR-V567es has been defined in xenografts originated from mCRPC upon extended administration of ADT, is over-expressed in tumoral tissues of xenografts that have obtained enzalutamide insensitivity, up-regulated in human metastatic tissues, and is included within de novo tumor development [25-27].

Observation of AR-V7 in Circulatory Tumor Cells (CTCs) has been correlated with insensitivity to enzalutamide and abiraterone. In a research of 62 patients with mCRPC exposed to abiraterone (n=31) or enzalutamide (n=31), 18 patients (6 taking abiraterone; 12 taking enzalutamide) had noticeable AR-V7 mRNA in their CTCs. The subjects with observable AR-V7 had no considerable Prostate-Specific Antigen (PSA) decreases and shorter median OS and Progression-Free Survival (PFS), when compared to the patients having no observable AR-V7. In a surveillance trial, these findings were more encouraged, although roughly 14% had leastwise 50% PSA decrease [28]. The detection of circulatory AR-V7 RNA outside CTCs has further been correlated with weaker results with enzalutamide and abiraterone [29]. In a molecular specification research, 37% of patients with mCRPC taking enzalutamide showed primary insensitivity. AR-V7 expression was more frequent in subjects with primary insensitivity (P=0.018) and AR-V7 was not detected in tumors from the subjects who had extended efficacy through enzalutamide therapy. This research presented a movement of AR from nucleus to cytoplasm, which associated with PSA decrease and raised testosterone concentration in patients upon enzalutamide therapy, proposing that enzalutamide inhibits AR signaling, besides activates adaptable feedback [30]. Different researches showed that down-regulation of AR-V7 in PC cell lines increments response to enzalutamide [31]. It has been proposed that ARv567es or AR-V7expressions trigger insensitivity to AR-targeted treatment modalities in case of ligand deficiency by generating dimers with full-body AR and enabling AR nuclear trafficking, thence reducing the efficacies of anti-androgen treatments to suppress AR nuclear localization [32].

Alternate signal transduction pathways

AR actions can be triggered by alternate signaling systems, numerous of which takes crucial functions within other human cancers' development [33]. Signaling system by NF-κB transcription factor has a certain function in CRPC progression by sustaining AR action and maintaining AR transcriptional and translational efficiency [34]. Moreover, its gene mark is adequate in anticipating survival specified to prostate cancer in clinical tests

[35]. Further substantial survival signaling systems (skipping AR-triggered instruments), like PI3K/AKT pathway, have been investigated in terms of transformation to metastatic CRPC and defined as supporters to progressed metastatic cancer [36]. Reduced activity of tumor suppressor PTEN and negative modulator of this system is one of the most common molecular changes in human prostate cancer. In fact, PTEN deficiency causes the advancement of AR signaling in a growth independent manner and the improvement of castration insensitivity is inherent and not unexpected on maintained AR action [37]. Additionally, PTEN state at diagnosis is prescient for both metastasis, prostate cancer-specific survival and time to CRPC, and reaction to ADT [38]. At last, growth factors like Keratinocyte Growth Factor (KGF), Epidermal Growth Factor (EGF) and Insulin-Like Growth Factor 1 (IGF-1) have been presented to immediately trigger AR in an androgen-independent manner [39].

Alternate co-activators

The AR is accepted to be associated with a plenty of co-repressors and co-activators, numerous of which take a function within the transformation to castration-insensitive form [21]. Co-activators improving AR action may practically conduce to increased sensitivity of AR for alternate ligands during the endogenous androgen deficiency [40]. For case, ARA70, the co-activator, may increment estradiol sensitivity of AR in prostate cancer cell lines [41]. A different co-activator, FKBP51, consolidates HSP90-AR complex, upgrading the capacity of AR molecules to recruit androgens [42]. Lastly, TRIM24 may be an oncogenic co-activator for transcription that has been appeared to conduce to AR signaling beneath castrate androgen levels in CRPC and in SPOP mutants [43]. In addition, a recent study showed that TRIM28 protein interacts with TRIM24 to inhibit its ubiquitin-dependent degradation by Speckle-type POZ protein (SPOP). By this way, TRIM28 enables TRIM24 availability on the chromatin and, as TRIM24, triggers AR signaling in aggressive resistant types of PC [44].

Conclusion

All in all, this chapter summarizes our actual comprehension of drug resistance mechanisms in transition to and after the castration resistance generation, emphasizing reversible and targetable pathways of insensitivity. Therapeutical approaches for advanced CRPC in clinic is hard because of the variety of insensitive clones, particularly in those resistant to various types of treatment options. The forthcoming PC treatment modality will probably contain both serial liquid biopsy to evaluate disease grade and search for extra functional targets, and tactical combinatorial treatment strategies triggering reversal of the insensitive characteristic.

References

1. Karantanos T, Evans CP, Tombal B, Thompson TC, Montironi R, et al. Understanding the mechanisms of androgen deprivation resistance in prostate cancer at the molecular level. Eur Urol. 2015; 67: 470-479.

2. Tan ME, Li J, Xu HE, Melcher K, Yong E-l. Androgen receptor: structure, role in prostate cancer and drug discovery. Acta Pharmacol Sin. 2015; 36: 3.

3. Crawford ED, Higano CS, Shore ND, Hussain M, Petrylak DP. Treating patients with metastatic castration resistant prostate cancer: a comprehensive review of available therapies. J Urol. 2015; 194: 1537-1547.

4. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. New Engl J Med. 2014; 371: 424-433.

5. Schmid SC, Geith A, Böker A, Tauber R, Seitz AK, et al. Enzalutamide after docetaxel and abiraterone therapy in metastatic castration-resistant prostate cancer. Adv Ther. 2014; 31: 234-241.

6. Krasnov G, Dmitriev A, Sadritdinova A, Volchenko N, Slavnova E, et al. Molecular genetic mechanisms of drug resistance in prostate cancer. Mol Biol. 2015; 49: 638-648.

7. Coffey K, Robson CN. Regulation of the androgen receptor by post-translational modifications. J Endocrinol. 2012; JOE-12-0238.

8. Gioeli D, Ficarro SB, Kwiek JJ, Aaronson D, Hancock M, et al. Androgen receptor phosphorylation Regulation and identification of the phosphorylation sites. J Biol Chem. 2002; 277: 29304-29314.

9. Ueda T, Bruchovsky N, Sadar MD. Activation of the androgen receptor N-terminal domain by interleukin-6 *via* MAPK and STAT3 signal transduction pathways. J Biol Chem. 2002; 277: 7076-7085.

10. Agoulnik IU, Vaid A, Bingman WE, Erdeme H, Frolov A, et al. Role of SRC-1 in the promotion of prostate cancer cell growth and tumor progression. Cancer Res. 2005; 65: 7959-7967.

11. Agoulnik IU, Vaid A, Nakka M, Alvarado M, Bingman WE, et al. Androgens modulate expression of transcription intermediary factor 2, an androgen receptor coactivator whose expression level correlates with early biochemical recurrence in prostate cancer. Cancer Res. 2006; 66: 10594-10602.

12. Fizazi K, De Bono J, Flechon A, Heidenreich A, Voog E, et al. Randomised phase II study of siltuximab (CNTO 328), an anti-IL-6 monoclonal antibody, in combination with mitoxantrone/prednisone *versus* mitoxantrone/prednisone alone in metastatic castration-resistant prostate cancer. Eur J Cancer. 2012; 48: 85-93.

13. Rossi J, Negrier S, James N, Kocak I, Hawkins R, et al. A phase I/II study of siltuximab (CNTO 328), an anti-interleukin-6 monoclonal antibody, in metastatic renal cell cancer. Brit J Cancer. 2010; 103: 1154.

14. Zhang X, Hong SZ, Lin EJ, Wang DY, Li ZJ, et al. Amplification and protein expression of androgen receptor gene in prostate cancer cells: Fluorescence in situ hybridization analysis. Oncol Lett. 2015; 9: 2617-2622.

15. Merson S, Yang Z, Brewer D, Olmos D, Eichholz A, et al. Focal amplification of the androgen receptor gene in hormone-naive human prostate cancer. Brit J Cancer. 2014; 110: 1655.

16. Mostaghel EA, Plymate SR, Montgomery B. Molecular pathways: targeting resistance in the androgen receptor for therapeutic benefit. Clin Cancer Res. 2014; 20: 791-798.

17. Von Klot CA, Kramer MW, Böker A, Herrmann TR, Peters I, et al. Is there an anti-androgen withdrawal syndrome for enzalutamide?. World J Urol. 2014; 32: 1171-1176.

18. Duan M, Liu N, Zhou W, Li D, Yang M, et al. Structural diversity of ligand-binding androgen receptors revealed by microsecond long molecular dynamics simulations and enhanced sampling. J Chem Theory Comput. 2016; 12: 4611-4619.

19. Liu C, Armstrong CM, Lou W, Lombard AP, Cucchiara V, et al. Niclosamide and bicalutamide combination treatment overcomes enzalutamide-and bicalutamide-resistant prostate cancer. Mol Cancer Ther. 2017; 16: 1521-1530.

20. Taplin M-E, Bubley GJ, Shuster TD, Frantz ME, Spooner AE, Ogata

GK, et al. Mutation of the androgen-receptor gene in metastatic androgen-independent prostate cancer. New Engl J Med. 1995; 332: 1393-1398.

21. Wang Q, Li W, Liu XS, Carroll JS, Jänne OA, et al. A hierarchical network of transcription factors governs androgen receptor-dependent prostate cancer growth. Mol Cell. 2007; 27: 380-392.

22. Cao B, Qi Y, Zhang G, Xu D, Zhan Y, et al. Androgen receptor splice variants activating the full-length receptor in mediating resistance to androgen-directed therapy. Oncotarget. 2014; 5: 1646.

23. Dehm SM. AR Alternative Splicing and Prostate Cancer Progression. In.: Minnesota Univ Minneapolis. 2012.

24. Sun S, Sprenger CC, Vessella RL, Haugk K, Soriano K, et al. Castration resistance in human prostate cancer is conferred by a frequently occurring androgen receptor splice variant. J Clin Invest. 2010; 120: 2715-2730.

25. Guo Z, Yang X, Sun F, Jiang R, Linn DE, et al. A novel androgen receptor splice variant is up-regulated during prostate cancer progression and promotes androgen depletion–resistant growth. Cancer Res. 2009; 69: 2305-2313.

26. Lu J, Van der Steen T, Tindall DJ. Are androgen receptor variants a substitute for the full-length receptor? Nat Rev Urol. 2015; 12(3):137.

27. Liu G, Sprenger C, Sun S, Epilepsia KS, Haugk K, et al. AR variant ARv567es induces carcinogenesis in a novel transgenic mouse model of prostate cancer. Neoplasia. 2013; 15: 1009-IN1003.

28. Antonarakis ES, Lu C, Luber B, Wang H, Chen Y, et al. Androgen receptor splice variant 7 and efficacy of taxane chemotherapy in patients with metastatic castration-resistant prostate cancer. JAMA Oncol. 2015; 1: 582-591.

29. Todenhöfer T, Azad A, Stewart C, Gao J, Eigl BJ, et al. AR-V7 transcripts in whole blood RNA of patients with metastatic castration resistant prostate cancer correlate with response to abiraterone acetate. J Urol. 2017; 197: 135-142.

30. Efstathiou E, Titus M, Wen S, Hoang A, Karlou M, et al. Molecular characterization of enzalutamide-treated bone metastatic castration-resistant prostate cancer. Eur Urol. 2015; 67: 53-60.

31. Liu C, Lou W, Armstrong C, Zhu Y, Evans CP, et al. Niclosamide suppresses cell migration and invasion in enzalutamide resistant prostate cancer cells *via* Stat3-AR axis inhibition. Prostate. 2015; 75: 1341-1353.

32. Xu D, Zhan Y, Qi Y, Cao B, Bai S, et al. Androgen Receptor Splice Variants Dimerize to Transactivate Target Genes. Cancer Res. 2015; 75: 3663-3671.

33. Yuan X, Cai C, Chen S, Yu Z, Balk S. Androgen receptor functions in castration-resistant prostate cancer and mechanisms of resistance to new agents targeting the androgen axis. Oncogene. 2014; 33: 2815.

34. Jin RJ, Lho Y, Connelly L, Wang Y, Yu X, et al. The nuclear factor-κB pathway controls the progression of prostate cancer to androgen-independent growth. Cancer Res. 2008; 68: 6762-6769.

35. McCall P, Bennett L, Ahmad I, Mackenzie L, Forbes I, et al. NFκB signalling is upregulated in a subset of castrate-resistant prostate cancer patients and correlates with disease progression. Brit J Cancer. 2012; 107: 1554.

36. Berger MF, Lawrence MS, Demichelis F, Drier Y, Cibulskis K, et al. The genomic complexity of primary human prostate cancer. Nature. 2011; 470: 214.

37. Carver BS, Chapinski C, Wongvipat J, Hieronymus H, Chen Y, et al. Reciprocal feedback regulation of PI3K and androgen receptor signaling in PTEN-deficient prostate cancer. Cancer Cell. 2011; 19: 575-586.

38. Lotan TL, Carvalho FL, Peskoe SB, Hicks JL, Good J, et al. PTEN loss is associated with upgrading of prostate cancer from biopsy to radical prostatectomy. Modern Pathol. 2015; 28: 128.

39. Craft N, Shostak Y, Carey M, Sawyers CL. A mechanism for hormone-independent prostate cancer through modulation of androgen receptor signaling by the HER-2/neu tyrosine kinase. Nat Med. 1999; 5: 280.

40. Kahn B, Collazo J, Kyprianou N. Androgen receptor as a driver of therapeutic resistance in advanced prostate cancer. Int J Biol Sci. 2014; 10: 588.

41. Miyamoto H, Yeh S, Wilding G, Chang C. Promotion of agonist activity of antiandrogens by the androgen receptor coactivator, ARA70, in human prostate cancer DU145 cells. P Natl Acad Sci. 1998; 95: 7379-7384.

42. Ni L, Yang C-S, Gioeli D, Frierson H, Toft DO, et al. FKBP51 promotes assembly of the Hsp90 chaperone complex and regulates androgen receptor signaling in prostate cancer cells. Mol Cell Biol. 2010; 30: 1243-1253.

43. Groner AC, Cato L, de Tribolet-Hardy J, Bernasocchi T, Janouskova H, et al. TRIM24 is an oncogenic transcriptional activator in prostate cancer. Cancer Cell. 2016; 29: 846-858.

44. Fong KW, Zhao JC, Song B, Zheng B, Yu J. TRIM28 protects TRIM24 from SPOP-mediated degradation and promotes prostate cancer progression. Nat Commun. 2018; 9: 5007.