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GENES AND CELL SIGNALLING IN PROSTATE CANCER: A REVIEW

Gregory Elayeche Oko[1]*, Emmanuel Paul Okoi[2], Maryam Ammani Lawal[3], Khuyen Thi Kim Vo[4], Margaret Akpana Odey[5] and Trung Minh Dao[6]

[1]Department of Biochemistry, College of Medical Sciences, University of Calabar; Nigeria, PMB 1115 Calabar.
[2]Department of Genetics and Biotechnology, Faculty of Biological Sciences, University of Calabar; Nigeria, PMB 1115 Calabar.
[3]Department of Pharmacy, Yusuf Dantsoho Memorial Hospital Tudun, Wada Kaduna-Nigeria.
[4]Institute of Environmental Science, Engineering and Management, University of Ho Chi Minh City, Vietnam.
[5]Department of Medicine and Surgery, Faculty of Medicine and Dentistry, University of Calabar; Nigeria, PMB 1115 Calabar.
[6]Faculty of Natural Sciences, Thu Dau Mot Univesity, Thu Dau Mot City, Binh Duong, Vietnam.

***Corresponding Author: Gregory Elayeche Oko**

Department of Biochemistry, College of Medical Sciences, University of Calabar; Nigeria, PMB 1115 Calabar.

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ABSTRACT

Cancer is a genetic disease linked with alteration or mutation of gene with multistep process for tumor development. The prostate cancer is globally rated as the second most common cancer. Typically, cancer occurs due to smoking and infectious diseases as well as chemicals and radiation. In this review we examine the function of various molecular and epigenetic genes associated with prostate cancer. An online search of current and past peer reviewed literature on cancer with emphasis on prostate was performed. We also discuss the functionality of the gland of prostate carryout by cell signalling. In conclusion, the various genes with diverse role at specific loci involved in prostate cancer are either overexpressed, down-regulated or inactivated at initiation stage or progression to metastasis with some being targeted for therapeutic purpose.

KEYWORDS: Prostate cancer**,** TMPRSS2 gene, GSTP1 gene, androgen receptor signalling.

INTRODUCTION

Cancer which is a genetic disease linked with alteration or mutation of gene with multistep process for tumor development is of great challenge to the world. Smoking, diet, and infectious diseases as well as chemicals and radiation along with trace levels of pollutants in food, drinking water and in air are some determinant factors for cancer initiation. In recent time, prostate cancer has become the most prevalent non-cutaneoues tumor type that occur in men. In Africa, Ferlay et al.,(2012) reported that Cancer incidence rates were 115.6 and 132.4 per 100,000 among men and women respectively. However, report have shown that mortality rate of prostate cancer are generally higher in predominantly black African populations compared to other races (Rebbeck et al., 2013). Globally, prostate cancer is rated the second most common cancer and sixth leading cause of death among men with estimation of 1.1millioncases and 300, 000 death in 2012(Baade et al.,2009; Bray et al., 2012; Ferlay et al.,2012). Siegel *et al.,*(2014), stated that, about 220,000 men resident in United State are diagnose with Pca and death incident of this disease estimated as 27,540 patient per annum. The molecular background of this tumor is still unclear but initiation and progression is traceable to elevated androgen signaling pathway (Jemal *et al.,* 2010).

The various gene ranging from P53, PTEN, NKx3.1, amplication and of AR, and methylation of tumor suppressor gene (GSTP) has play a vital role in prostate cancer. However, the fusion and activation of transcriptional program which has upregulate expression of MYC, EZH2, and Sox9 along with repressing of NKx3.1 is initiated by increased expression of ERG factor at the influence of androgen responsive promoter. Despite the roles of various genes in prostate cancer along with deprivation therapy of androgen being the main pillar for treatment, prostate cancer remain the largely incurable disease of the world(Kim and Yu, 2012). This review focused on the roles of genes implicated in prostate cancer and the functionality of prostate cancer by cell signalling.

Molecular and Epigenetic Pathway in Prostate Cancer

The metastasis formation is usually linked to a precursor called prostatic intraepithelial with several genes such as; Nkx.1, Myc, TMPRSS2-ERG, EZH2 PTEN implicated

as shown in Fig(1) are either over-expresssed, down-regulated, or inactivated.

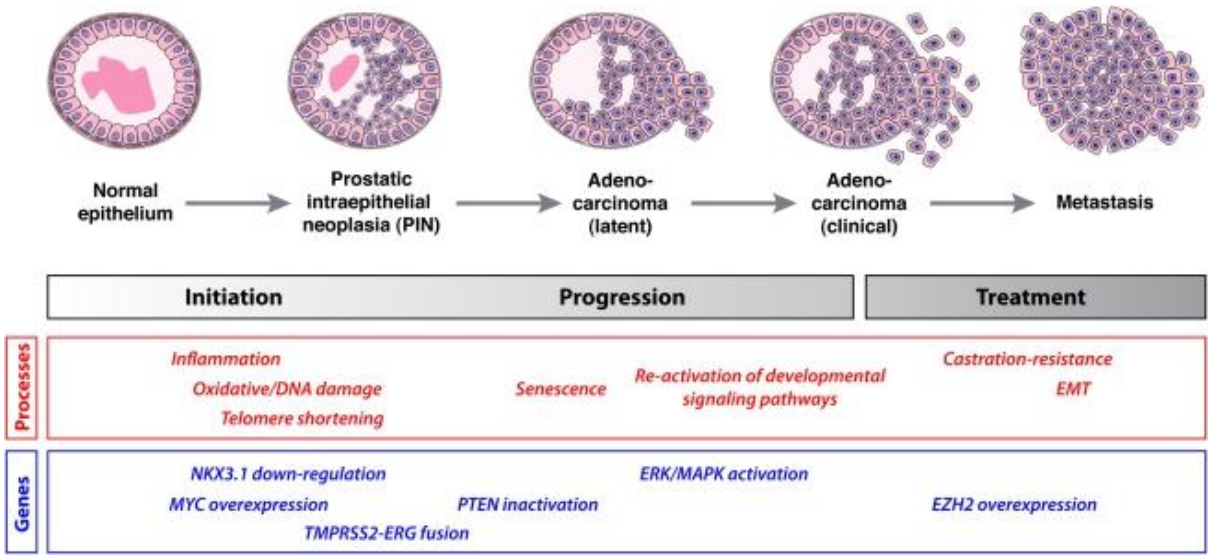

Fig. 1: Recognition and advancement pathway of Pca (Abate-shen and Shen, 2000).

Homeobox protein(Nkx3.1)

The Nkx3.1 gene located within 8p21.2 chromosome of human act as trancriptional factor with a unique function in the development of prostate and suppression of tumor. The transcriptional activation is enhanced when NKX3.1 binds to DNA by suppressing transcriptional processes along with interaction of serum response factor. However, when this gene is mutated they is loss of up to 89% of high graded PIN and prostatic adenocarcinomas which may be attributed to post-transcriptional silencing, methylation, and allelic loss (Gurel *et al.*,2010; Abate-shen et al.,2008). Thus, in the initiation of cancer in both genetically engineered mice and human tumor, NKX3.1 gene causes an inactivation in mice resulting to defective oxidative damage response. Whereas, human tumor expression of Nkx3.1 leads to protection against DNA damage (Bowen and Gelman, 2010; Markowski *et al.*,2008).

Master of transcription regulation (**Myc)**

The Myc gene being a regulator that is coded for transcriptional factor that function in the progression of cell cycle, cellular transformation and apoptosis can be mutated leading to overexpression (fig1) (Gearhart *et al.*,2007). The overexpression of MYC can be traced to amplication of gene 8q24 which was verify using fluorescence in situ hybridization on 44 prostatectomy samples with resultant 8 out of 9 cases showing amplication of gene 8q24(VanDen *et al.,* 1995). Wang *et al.,(*2009), reported that, FoxP3 x-linked gene encoded with winged helix transcription factor involved in repression of MYC expression is usually mutated in prostate cancer. However, MYC has become a targeted site for therapeutic purpose for prostate cancer by employing vitamin D, cardenolides and oligonucleotides antisense (Koh *et al.,* 2010). The antisense oligonucleotides has been found to decreased invivo prostate cancer cell viability and proliferation suppression but upon testing for potency with xenographs murine in prostate cancer; a size reduction of tumor was discovered resulting from apoptosis and growth inhibition (Devi *et al.*,2005; Balaji *et al.*,1997).

TMPRSS2

The TMPRSS2 gene encoded by protein belonging to a family of serine protease depend on over expression of ERG, ETV1, and ETV4 (transcriptional factor) via fusion of gene to function effectively in prostate carcinogenesis. The 40% to 60% of prostate cancer can be attributed to TMPRSS2-ERG Fusion via interchromosomal rearrangement and ERG overexpression promotes androgen independence development in Pca via signal interruption of AR (Yu *et al.*,2010; Tomlin *et al.*,2005). The fusion process of TMPRSS-ERG which occur via break of double-stranded DNA is seen as early event found in PIN and as initiator of PIN has contributed in upregulating expression of SOX9 and EZH2 with a repression of NKX3.1(Cai *et al.*,2013; Kunderfranco *et al.,* 2010; Mani *et al.,* 2009; Klezovitch *et al.,* 2008). Yu *et al.,(*2010), shown that, upon binding of ERG with downstream target gene of AR using a whole genome disruption of signaling pathway of AR that occur in prostate cancer cells via epigenetic silencing is vital in prevention of prostate epithelium differentiation. The ETS family transcriptor factors has no targeted site for drugs but via preclinical studies, an inhibitor of deubiquinatin enzyme USPAX compound WP1130 has shown a growth restrains in invivo and invitro in prostate cancer(Wang *et al.,* 2014). It is also believed that, fusion of ETS positive PCa patient can benefit from poly(ADP-ribose) and polymerase 1 inhibitor due to interactions of TMPRSS-ERG with DNA protein kinase subunit and PARP-1(Brenner *et al.*,2011).

Phosphatase and Tensin Homolog(PTEN)

The PTEN which is a dual specific protein and lipid phophatase with cellular substrate called phosphatidylinositol 3, 4, 5 trisphosphate(PIP3) blocks phosphatidylinositol 3 kinase signaling via inhibition of PIP3 dependent processes thereby leading to prevention of cell survival, growth, proliferation and cellular migration(Leslie *et al.*,2007; Maehama and Dixon, 1998). It is believed that, PTEN being mutated in prostate cancer and loss was traced to 10q23 region of chromosome that undergoes allelic loss, and reduction of tumor expression (Salmena et al., 2008; Whang *et al.*,1998). The parallels observations of NKX3.1 deficiency and the regulatory cell cycle of P^{27} is linked with low level of PTEN activities which may be retained in PCa when undergoing series of lose copy at the early stage of tumorigenesis (Abate-shen *et al.*, 2008). However, inactivations of PTEN can cooperate with loss of role play by TMPRSS-ERG fusion, NKX3.1 gene or c-MYC upregulation(Kim *et al.*, 2009; King *et al.*,2009; Wang *et al.*,2003). As PTEN becomes mutated they is tendency for deregulation of protein synthesis, migration, and cell survival (Hopkins *et al.*,2014).

Enhancer of Zeste Homolog2(EZH2)

The EZH2 being a histone lysine N-methylstransferase enzyme plays a vital role in methylation of DNA and transcriptional process (Vire et al., 2006). EZH2 as a component of PRC2 that is usually overexpressed(fig 1) along with high graded PIN promotes proliferation, and tumorigenicity (Simon and Lange, 2008; Saramaki *et al.*,2006). The upregulational activity of EZH2 is traced to amplication of gene via deletion or family member of ETS via transcriptional regulation(Yu et al.,2010; Varambally *et al.*,2008; Saramaki *et al.*,2006). Nevertheless, inhibition of genes responsible for suppressing tumor development by EZH2 and blockade of it activities may lead to slow tumor growth(Kim and Roberts, 2016).

Glutathione S-transferase promoter gene (GSTP1)

The GSTP1 on chromosome 11q13 help in the protection of cells from cytotoxics and carcinogenic carrier (Meiers *et al.*,2007). Altered GSTPI activity and expression which is due to hypermethylation of DNA at CPG island in promoter 5´ is noticed in 70% of PIN a precursor for metastasis (Li, 2007; Elo and Visakorpi, 2001; Brook *et al.*,1998). It is believed that, the GSTP1 enzyme help in detoxifying cells leading to protection against carcinogen. But GSTP1 promoter being hypermethylated will disturb defensive role of GSTP1 enzymes thereby predisposing cells to subsequent genetic aberration (Elo and Visakorpi, 2001). Henrique et al.,(2006), stated that, changes from PIN to carcinoma is primarily due to high levels of GSTP1 promoter methylation. However, modification of Promoter which is reversible when compare to genetic alteration that permanently change DNA sequence can be easy to therapeutic invasion with the aim of reactivating silenced cancer genes (Meiers *et al.*,2007).

Intracellular Cell Signaling In Prostate Cancer

The functionality of the gland of prostate can be carryout by cell signaling. Reynolds and Kyprianou,(2006), stated that; cell growth which is controlled by FGF and IGF-1, Transforming growth factor-β that command apoptotic effect, and diverse signaling pathways are implicated in prostate cancer.

Androgen receptor signaling

The androgen receptor positioned on Xq11-Xq12 X chromosome that binds with androgenic hormones, testosterone, and dihydrotestosterone is primarily concerned in the modulation of cell cycle, adhesion, apoptosis, metabolism, and ECM remodeling through modulation of transcriptional genes in human prostate(Heinlein and Chang, 2004). The binding of Testosterone or DHT with ligand at the cytoplasm causes the release of AR from the heat shock protein which would be translocated to the nucleus, dimerized and then androgen response element from chromatin bind in the promoter region of targeted genes(example; PSA and TMPRSS2) leading to recruitment of transcriptional factor including complexes of chromatin remodelling, histone acetyl ttransferase activity(CBP), coactivator and RNA polymerase11 causing a cell growth differentiation(KaarbѲ *et al.*,2007). The AR also induces transcription of various genes of human prostate such as; cylin-dependent kinase 1A(P21), Prostate specific Antigen, Kallikrien 3 and matrix metalloproteinase-2(MMP-2) (Heinlein and Chang, 2002). AR gene amplication and overexpression in prostate cancer can also be a potential therapeutic target. It is believed that, closure of androgen receptor pathway would be enough for inducing tumor relapse since most prostate cancer are responsive to androgen stimulation for initial growth(Yang *et al.*,2005; Visakorpi,2003). For instance, at the early stage of malignant transformation AR signalling activated by androgen can change from paracrine to autocrine and making the patients to have a very decreased level of testosterone and highly expressed AR levels(Vander-Griend *et al.*,2010; Gao *et al.*,2001). This can be attributed to gain of function mutation or amplication in AR genes, derived active form from AR proteolytic processing, cofactors of androgen receptors, deregulation, and tyrosine kinase receptor and growth factors (Meyer *et al.*,2004; Buchannan *et al.*, 2001; Kang *et al.*,2001).

Transforming Growth Factor-β(TGF-β)

The TGF-β being a super family member of cytokines are concerned for controlling different physiological processes varying from, organogenesis, angiogenesis, adhesion, Chemotaxis, cell proliferation, differentiation, to apoptosis(Korrodi-Gregorio *et al.*,2012). The TGF-β binds to type 1 & 11 TGF-β receptors(heterodimeric receptors) thereby activating smads pathways via MAPK, p13k and Akt. The TGF-β1 is mostly expressed in adult prostate gland when compared to its isoforms (TGF-β2 &TGF-β3) that acts mainly within a normal epithelial cell as tumor suppressor; but at the

advancement to metastasis in prostate cancer, withdrawal of androgen may cause overexpression of TGF-β1 leading to oncogenesis enhancement (Zhu and Kyprianou, 2008; Bello-DeOcampo and Tindall, 2003; Derynck and Zhang,2003). Zhu and Kyprianou,(2008) stated that; in the absent of DHT that AR expression will be directly down-regulated or transcriptional activities of TGF-β1 signaling would be inhibited with resultant decreases of its growth effects.

Phosphoinositide-3-Kinases /Akt Signaling

The signaling pathway by p13k/Akt control cell cycle and also plays a vital function in proliferation of cell and survival upon being phosphorylated. The mediation of cell cycle advancement and cyclin visibility is via activation of Akt targeted of rapamycin signalling in prostate cancel cells pathway(Gao *et al.*,2003). Bellacosa and Larue (2010), showed that; PAkt regulates EMT and cell invasion upon inducing the production of desmoplakin, vitamin, and metaloproteinases.

Wnt Pathway

Wnt production in Prostate cancer bone mestatasis tend to stimulates osteoblast differentiation thereby exerting autocrine effects in proliferation of pca (Hall *et al.*,2006). the wnt is capable of binding with frizzled family mainly the cell surface receptors and activates members of dishevelled family. The complexes formed by wnt/frizzed family leads to stabilization of β- catenin which will be translocated to the nucleus thereby promoting multiplex downstream signalling (Ziaee *et al.*,2014).

CONCLUSION

The variou genes with diverse role at specific loci involved in prostate cancer are either overepressed, down-regulated or inactivated at the initiation stage or on progression to metastasis with some being targeted for therapeutic purpose. However, Transforming growth factor with several cell signalling are been implicated for promoting cell proliferation, apoptotic effect and survival thereby potentiating tumor regulation.

List of Abbreviations

Akt1 Central kinase in p13k pathway
AR Androgen receptor
DHT Dihydrotestosterone
ECM Extracellular Matrix
EMT Epithelial Mesenchymal transition
ETS Early tumour Shrinkage
MAPK mitogen Activated Protein Kinase
Pca Prostate Cancer
PIN Prostatic intraepithelial neoplasia
P13 Phosphoinositide -3- kinase
P^{53} Tumor Suppressor
P^{27} Cyclin-dependent Kinase inhibitor
PSA prostate Specific Antigen
PRC2 Polycomb Repressive Complex 2
SOX9 Prostate Stem Cells homeobox
TMPRSS2: ERG gene fusion involving EGR

REFERENCES

1. Abate-Shen, C., and Shen, M.M. (2000). Molecular genetics of prostate cancer. *Genes Dev*, 14: 2410-2434.
2. Abate-Shen, C., Shen, M.M., and Gelmann, E. (2008). Integrating differentiation and Cancer. The Nkx3.1 homeobox gene in prostate organogenesis and carcinogenesis. *Differentiation*, 76: 717-727.
3. Baade, P.D., Youlden, D.R., a and KrnJack, I.J. (2009). International Epidiomology of Prostate Cancer: Geographical distribution and secular trends. Molecular Nutrition and Food Research., 53(2): 171-178.
4. Balaji, K.C, Koul, H., Mitra, S., Maramag, C., Reddy, P., Menon, M., Malhotra, R.K., and Laxmanan, S. (1997). Antiproliferative effects of c-myc antisense oligonucleotide in prostate cancer cells: a novel therapy in prostate cancer. *Urology*, 50(6): 1007-15.
5. Bellacosa, A., and Larue, L. (2010). P13k/AKT pathway and epithelial-mesenchymal transition. In: Thomas-Tikhonenko, A.(ED), Cancer Genome and Tumor Microenvironment. Springer, New York, 11-32.
6. Bello-DeOcampo, D., and Tindall, D.J. (2003). TGF-β/Smad signalling in prostate cancer. *Curr. Drug Targets*, 4(3): 197-207.
7. Bowen, C., and Gelman, E.P. (2010). Nkx3.1 activates cellular response to DNA damage. *Cancer Res*, 70: 3089-3097.
8. Bray, F., Jemal, A., Grey, N., Ferlay, J., and Forman, D. (2012). Global cancer transitions according to human development index(2008-2030): A population based study. Lancet Oncol., 13: 790-801.
9. Brenner, J.C., Ateeq, B., Li, Y., Yocum, A.K., Cao, Q., Asangani, I.A., Patel, S., Wang, X., Liang, H., Yu, J., Palanisamy, N., Siddiqui, J., Yan, W., Cao, X., Mehra, R., Sabolch, A., Bashur, V., Lonigro, R.J., Yang, J., Tomlins, S.A., Maher, C.A., Elenitoba-Johnson, K.S., Hussain, M., Navone, N.M., Pienta, K.J., Verambally, S., Feng, F.Y., and Chinnaiyan, A.M. (2011). Mechanistic rationale for inhibition of Poly(ADP-ribose) polymerase in ETS gene fusion-positive in prostate cancer. *Cancer Cell*, 19(5): 664-678.
10. Brooks, J.D., Weinstein, M., Lin, X., Sun, Y., Pin, S.S., Bova, G.S., Epstein, J.I., Isaacs, W.B., and Nelson, W.B. (1998). CG island methylation changes near the G GSTP1 gene in prostatic intraepithelial neoplasia. *Cancer Epidemiol. Biomarkers Prev*., 7(6): 513-6.
11. Buchanan, G., Greenberg, N.M., Scher, H.I., Harris, J.M., Marshall, V.R., and Tilley, W.D. (2001). Collocation of androgen receptor gene mutations in prostate cancer. *Clin. Cancer Res.*, 7(5): 1273-1281.
12. Cai, C., Wang, H., He, H.H., Chen, S., He, L., Ma, F., Mucci, L., Wang, Q., Fiore, C., Sowalky, A.G., Loda, M., Lui, X.S., Brown, M., Balk, S.P., and Yuan, X. (2013). ERG induces androgen receptor-

mediated regulation of SOX9 in prostate cancer. *Journal of Clinical investigation*, 123(3): 1109-1114.
13. Derynck, R., and Zhang, Y.E. (2003). Smad-dependent and Smad-independent pathways in TGF-beta family signalling. *Nature*, 425(6958): 577-84.
14. Devi, G.R., Beer, T.M., Corless, C.L., Arora, V., Weller, D.L., and Iversen, P.L. (2005). In vivo bioavailability and pharmacokinetics of a c-Myc antisense phosphorodiamidate morpholino oligomer, AVI-4126, in solid tumors. *Clin. Cancer Res.*, 11(10): 3930-8.
15. Elo, J.P., and Visakorpi, T. (2001). Molecular genetics of prostate cancer. *Ann. Med*., 33: 130-141.
16. Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., et al.,(2015). Cancer incidence and Mortality Worldwide: Sources, Methods and Major patterns in GLOBOCAN 2012. International Journal of Cancer, 136: E359-E89.
17. Gao, J., Arnold, J.T., and Isaacs, J.T. (2001). Conversion from a paracrine to an autocrine mechanism of androgen stimulated growth during malignant transformation of prostatic epithelial cells. *Cancer Res.*, 61(13): 5038-5044.
18. Gao, N., Zhang, Z., Jiang, B.H., and Shi, X. (2003). Role of PI3K/AKT/mTOR signaling in the cell cycle progression of human prostate cancer. *Biochem. Biophys. Res. Commun*., 310(4): 1124-1132.
19. Gearhart, J., Pashos, E.E., and Prasad, M.K. (2007). Pluripotency redux-advances in stem cells research. *N. Engl. J. Med.*, 357(15): 1469-72.
20. Gurel, B., Ali, T.Z., Montgomery, E.A., Begum, S., Hicks, J., Goggins, M., Eberhart, C.G., Clark, D.P., Bieberich, C.J., Eptein, J.I., and DeMarzo, A.M. (2010). NKX3.1 as marker of prostatic origin in Metastatic tumors. *Am. J. Surg. Pathol.*, 34(8): 1097-1105.
21. Hall, C.L., Kang, S., MacDougald, O.A., and Keller, E.T. (2006). Role of wnts in prostate cancer metastases. *J. Cell Biochem*., 97(4): 661-72.
22. Heinlien, C.A., and Chang, C. (2002). Androgen receptor(AR) coregulators: an overview. *Endocr. Rev.*, 23(2): 175-200.
23. Heinlein, C.A., and Chang, C. (2004). Androgen receptor in prostate cancer. *Endocr. Rev.*, 25(2): 276-308.
24. Henrique, R., Jernimo, C., Teixeira, M.R., Hoque, M.O., Carvalho, A.L., Pais, I., Ribeiro, F.R., Oliveira, J., Lopes, C., and Sidransky, D. (2006). Epigenetic heterogeneity of high-grade prostatic intraepithelial neoplasia: clues for clonal progression in prostate carcinogenesis. *Mol. Cancer Res.*, 4(1): 1-8.
25. Hopkins, B.D., Hodakoski, C., Barrows, D., Mense, S.M., and Parsons, R.E. (2014). PTEN function: the long and short of it. Trends in Biochemical Sciences, 39(4): 183-190.
26. Jemal, A., Siegel, R., Xu, J., and Ward, E. (2010). Cancer Statistic. *CA cancer J. Clin.*, 60(5): 277-300.
27. KaarbΘ, M., Klokk, T.I., and Saatcioglu, F. (2007). Androgen Signaling and its interactions with signaling pathways in prostate cancer. *Bio Essays*, 29(12): 1227-1238.
28. Kang, H.Y., Lin, H.K., Hu, Y.C., Yeh, S., Huang, K.E., and Chang, C. (2001). From transforming growth factor-beta signalling to androgen action: identication of smad3 as an androgen receptor coregulator in prostate cancer cells. *Proc. Natl. Acad. Sci.*, 98(6): 3018-3023.
29. Kim, J., and Yu, J. (2012). Interrogating genomic and epigenomic data to understand prostate cancer. *BBA-Reviews on Cancer*, 1825(2): 186-96.
30. Kim, J., Eltoum, I.E., Roh, M., Wang, J., and Abdulkadir, S.A. (2009). Interactions between cells with distinct mutation in c-MYC and PTEN in prostate cancer. *PLOS genetics*, 5(7): e1000542.
31. King, J.C., Xu, J., Wongvipat, J., Heironymus, H., Carver, B.S., Leung, D.H., Taylor, B.S., Sander, C., Cardiff, R.D., Couto, S.S., Gerald, W.L., and Sawyers, C.L. (2009). Cooperativity of TMPRSS2-ERG with P13-kinase pathway activation in prostate oncogenesis. *Nat. Genet*, 41(5): 524-526.
32. Kim, K., and Roberts, C. (2016). Targeting EZH2 in cancer. *Nature Medicine*, 22: 128-134.
33. Klezovitch, O., Risk, M., Coleman, I., Lucas, J.M., Null, M., True, L.D., Nelson, P.S., and Vasioukhin, V. (2008). A causal role for ERG in neoplastic transformation of prostate epithelium. *Proc. Natl. Acad. Sci.*, 105(6): 2105-10.
34. Koh, C.M., Bieberich, C.J., Dang, C.V., Nelson, W.G., Yegnasubramanian, S., and De Marzo, A.M. (2010). MYC and prostate cancer. *Genes and Cancer*, 1(6): 617-628.
35. Korrodi-Gregorio, L., Teixeira, A.L., and Medeiros, R. (2012). TGFβ pathway. *In:* Fardilha, M., Da Cruz, E., Silva, O.A. (Eds). Essentials of cell signalling. Afrontamento, Aviero, 199-234.
36. Leslie, N.R., Yang, X., Downes, C.P., and Weijer, C.J. (2007). Ptdlns(3,4,5) P3-dependent and independent roles of PTEN in control of cell migration. *Curr. Biol.*, 17(2): 115-125.
37. Li, L.C. (2007). Epigenetics of prostate cancer. *Front Biosci.*, 12: 3377-3397.
38. Maehama, T., and Dixon, J.E. (1998). The tumor suppressor, PTEN/MMACI, dephosphorylates of lipid second messenger, phosphatidylinositol 3,4,5-trisphosphate. *J. Biol. Chem.*, 273(22): 13375-13378.
39. Mani, R.S., Tomlins, S.A., Callahan, K., Ghosh, A., Nyati, M.K., Varambally, S., Palanisamy, N., and Chinnaiyan, A.M. (2009). Induced chromosomal proximity and gene fusions in prostate cancer. *Science*, 326(5957): 1230.
40. Markowski, M.C., Bowen, C., and Gelman, E.P. (2008). Inflammatory cytokines induce phosphorylations and ubiquitination of prostate suppressor protein NKX3.1. *Cancer Res.*, 68(17): 6896-6901.

41. Meiers, I., Shanks, J.H., and Bostwick, D.G. (2007). Glutathione S-transferase pi (GSTP1) hypermethylation in prostate cancer. *Pathology*, 39(3): 299-304.
42. Meyer, H.A., Ahrens-Fath, I., Sommer, A., and Haendler, B. (2004). Novel molecular aspects of prostate carcinogenesis. *Biomed. Pharmacother.*, 58(1): 10-16.
43. Murray, P.J. (2007). The JAK-STAT signalling pathway: input and output integration. *J. Immunol.*, 178(5): 2623-9.
44. Rebbeck T.R., Devesa, S.S., Chang, B., Bunker, C.H., Cheng, I., Cooney, K. Et al., (2013). Glaobal Patterns of Prostate Cancer incidence, Aggressiveness, and Mortality in Men of African. Prostate Cancer, 2013: 560857.
45. Reynolds, A.R., and Kyprianous, N. (2006). Growth factor signaling in prostatic growth: significance in tumor development and therapeutic targeting. *Brit. J. Pharmacol.*, 147(S2): S144-S152.
46. Salmena, L., Carracedo, A., and Pandolfi, P.P. (2008). Tenets of PTEN tumor suppression. *Cell*, 133(3): 403-414.
47. Saramaki, O.R., Tammela, T.L., Martikainen, P.M., Vessella, R.L., and Visakorpi, T. (2006). The gene for polycomb group protein enhancer of zeste homolog 2 (EZH2) is amplified in late- stage prostate cancer. *Genes Chromosomes Cancer*, 45(7): 639-45.
48. Siegel, R., Ma, J., Zou, Z., and Jemal, A. (2014). Cancer statistics. *CA cancer J. Clin.*, 64(1): 9-29.
49. Simon, J.A., and Lange, C.A. (2008). Roles of the EZH2 histone methyltransferase in cancer epigenetics. *Mutat. Res.*, 647(2): 21-9.
50. Tomlins, S.A., Rhodes, D.R., Perner, S., Dhanasekaran, S.M., Mehra, R., Sun, X.W., Varambally, S., Cao, X., Tchinda, J., Kuefer, R., Lee, C., Montie, J.E., Shah, R.B., Pienta, K.J., Rubin, M.A., and Chinnaiyan, A.M. (2005). Recurrent fusion of TMPRSS2 and ETS transcription factor gene in prostate cancer. *Science*, 310(5748): 644-648.
51. VanDen, B.C., Guan, X.Y., Von, H.D., Jenkins, R., Bittner, G.C., and Kallioniemi, O. (1995). DNA sequence amplication in human prostate cancer identified by chromosome micro-dissection: potential prognostic implications. *Clin. Cancer Res.*, 1(1): 11-18.
52. Vander-Griend, D.J., D´Antonio, J., Gurel, B., Anthony,L., Dermazo, A.M., and Isaacs J.T. (2010). Cell-autonomous intracellular androgen receptor signalling drives the growth of human prostate cancer initiating cells. *Prostate*, 70(1): 90-99.
53. Varambally, S., Laxman, B., Mehra, R., Cao, I., Dhanasekaran, S.M., Tomlins, S.A., Granger, J., Vellaichamy, A., Sreekumar, A., Yu, J., Gu, W., Shen, R., Gosh, D., Wright, L.M., Kladney, R.D., Kuefer, R., Rubin, M.A., Fimmel, C.J. and Chinniayan A.M. (2008). Golgi protein GOLMI is a tissue and urine biomarker of prostate cancer. *Neoplasia*, 10(11): 1285-1294.
54. Vire, E., Brenner, C., Deplus, R., Blanchon, L., Fraga, M., Didelot, C., Morey, L., Eynde, A.V., Bernard, D., Vanderwinden, J., Bollen, M., Esteller, M., Croce, L.D., Launoit, Y., and Fuks, F. (2006). The Polycomb group protein EZH2 directly control DNA methylation. *Nature*, 439: 871-874.
55. Visarkorpi, T. (2003). The molecular genetics of prostate cancer. *Urology*, 62(suppl 5A): 3-10.
56. Wang, S., Gao, J., Lei, Q., Rozengurt, N., Pritchard, C., Jiao, J., Thomas, G.V., Li, G., Roy-Burman, P., Nelson, P.S., Liu, X., and Wu, H. (2003). Prostate specific deletion of the murine PTEN tumor suppressor gene leads to metastatic prostate cancer. *Cancer Cell*, 4(3): 209-221.
57. Wang, L., Lui, R., Li, W., Chen, C., Katoh, H., Chen, G.Y., McNally, B., Lin, L., Zhou, P., Zuo, T., Cooney, K.A., Lui, Y., and Zheng, P. (2009). Somatic single hits inactivate the X-linked tumor suppressor FOXP3 in the prostate. *Cancer Cell*, 16(4): 336-346.
58. Wang, S., Kollipara, R.K., Srivastava, N., Li, R., Ravindranathan, P., Hernandez, E., Freeman,E., Humphries, C.G., Kapur, P., Lotan, Y., Fazli, L., Gleave, M.E., Plymate, S.R., Raj, G.V., Hsiesh, J.T., and Kittler, R. (2014). Ablation of the oncogenic transcription factor ERG by deubiquitinase inhibition in prostate cancer. *Proc. Natl. Acad. Sci.*, 111(11): 4251-4256.
59. Whang, Y.E., Wu, X., Suzuki, H., Reiter, R.E., Tran, C., Vessella, R.L., Said, J.W., Isaacs, W.B., and Sawyer, C.L. (1998). Inactivation of tumor suppressor PTEN/MMACI in advanced human prostate cancer through loss of expression. *Proc. Natl. Acad. Sci.*, 95(9): 5246-5240.
60. Yang, Q., Fung, K.M., Day, W.V., Kropp, B., and Lin, H. (2005). Androgen receptor signalling is require for androgen-sensitive human prostate cancer cell proliferation and survival. *Cancer Cell Int.*, 5(1): 8-14.
61. Yu, J., Mani,R.S., Cao, Q., Brenner, C.J., Cao, X., Wang, X., Wu, L., Li, J., Hu, M., Gong, Y., Cheng, H., Laxman, B., Vellaichamy, A., Shankar, S., Li, Y., Dhanasekaran, S.M., Morey, R., Barrette, T., Lonigro, R.J., Tomlins, S.A., Varambally, S., Qin, Z.S., and Chinnaiyan, A.M. (2010). An integrated network of androgen receptor, polycomb, and TMPRSS2-ERG gene fusions in prostate cancer progression. *Cancer Cell*, 17(5): 443-454.
62. Zhu, M.L., and Kyprianou, N. (2008). Androgen receptor and growth factor signalling cross-talk in prostate cancer cells. *Endocrine-Related Cancer*, 15(4): 841-849.
63. Ziaee, S., Chu, G.C., Huang, J., Sieh, S., and Chung, L.W.(2014). Prostate cancer metastasis: roles of recruitment and reprogramming, cell signal network and three-dimensional growth characteristics. *Transl. Androl. Urol.*, 4(4): 438-454.