Chapter 1

Genetics in the Prostate Cancer

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Abstract

Any disruption in the intracellular functions ranging from DNA transcription to protein ligand binding as well as intercellular communication may cause cellular transformation to malignant cell in the proper microenvironment when it could escape from the immune system. In this chapter, specifically, genetic alterations playing role in the prostate cancer are intended to be reviewed briefly under the subheadings of genomic instability and the hallmarks of cancer which are sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling the replicative immortality, inducing angiogenesis, activating invasion and progression to metastatic disease, reprogramming of the energy metabolism and evading immune destruction.

Keywords: prostate, cancer, genetics, gene, carcinogenesis

1. Introduction

The basic molecular pathways and genetic alterations related to the cancer formation from normal cells irrespective of origin of tissue, are explained elsewhere in detail in many relevant textbooks. In this chapter, specifically, genetic alterations playing role in the prostate cancer are intended to be reviewed briefly under the subheadings of the hallmarks of cancer proposed by Hanahan and Weinberg, in the light of up to date studies [1, 2].

The proposed hallmarks of cancer are consisted of sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis, reprogramming of energy metabolism and evading immune destruction [1, 2]. Underlying these hallmarks is the genome instability, which generates the genetic diversity promoting their acquisition [1, 2].

The Cancer Genome Atlas (TCGA) research on prostate cancer figured out seven genetic subtypes of prostate cancer [3]. Four subtypes are characterized by specific gene fusions including whereas the rest are characterized by genetic mutations particularly in SPOP, FOXA1, and IDH1 genes [3]. Gene fusions mainly included ERG (46%), ETV1 (8%), ETV4 (4%), FLI1 (1%) and gene mutations were commonly found in SPOP (11%), FOXA1 (3%) and IDH1 (1%) [3]. However, still almost quarter percent are not categorized in any of them, confirming genetic heterogenicity of prostate cancer [3]. However, these recently suggested genetic subgroups of prostate cancer may fit for future clinical trials of selective medical or genetic treatments in relevant subgroups. Yet, it is to be noted that the presented classification does not necessarily mean the relevant genes either involving gene fusions or mutations are themselves cause of cancer formation and yet they may only represent common alterations during carcinogenesis driven by any other one.

In other words; any disruption in the intracellular functions ranging from DNA transcription to protein ligand binding as well as intercellular communication may cause cellular transformation to malignant cell in the proper microenvironment when it could escape from immunity.

2. Genomic instability

Using allelotyping except the short arms of the acrocentric chromosomes, loss of heterozygosity and or gene fusions were shown to be 61% in prostate cancer [4]. Common allelic deletions were in chromosome 16q (60%), chromosome 8p (50%), chromosome 10p (55%) and 10q (30%). Allelic deletions of chromosomes 2, 3, 7, 12, 13, 17, 18, 22, X and Y were at lower frequencies, however no allelic deletions were present in any case without any of the deletions in chromosomes 8, 10, or 16 [4–7]. As expected, the more chromosomal deletions were present, the higher histological grade was present in prostate cancer [4]. This genetic heterozygosity more has recently been confirmed by TCGA research as the gene fusions were reported in 59% of prostate cancer [3]. With more specific methods, deletion in some specific regions of chromosome 8p (specifically 8p11-8p21) is more common up to 50–70% in prostate cancer compared to others [4, 5, 8, 9]. Chromosomal region 8p11-8p21 contains over 400 genes (**Figure 1**) among which some has gained more attention in research for prostate carcinogenesis like NKX3.1 which is an androgen regulated prostate specific homeobox gene [10–12]. Conditional deletion of one or both alleles of Nkx3.1 in mice has been shown to cause prostatic intraepithelial neoplasia (PIN) [13]. Even in murine epigenetic cancer models, Nkx3.1 deficiency further increased the frequency of PIN lesions [14].

Another chromosomal alteration commonly seen, occur in chromosome 10 [4, 5, 15–19]. One of the common alterations (60%) is the loss of the phosphatase and tensin homolog gene (PTEN) on chromosome 10q23.3 which is a negative regulator of the PIK3/Akt survival pathway [15–19]. The loss of PTEN in prostate cancer has been linked to higher Gleason grades, oncogenic TMPRSS2-ERG fusions, androgen-independent progression and metastasis [15–19]. Else, the size of PTEN deletions were classified into five distinct subtypes: (1) small interstitial (70 bp–789 kb); (2) large interstitial (1–7 MB); (3) large proximal (3–65 MB); (4) large terminal

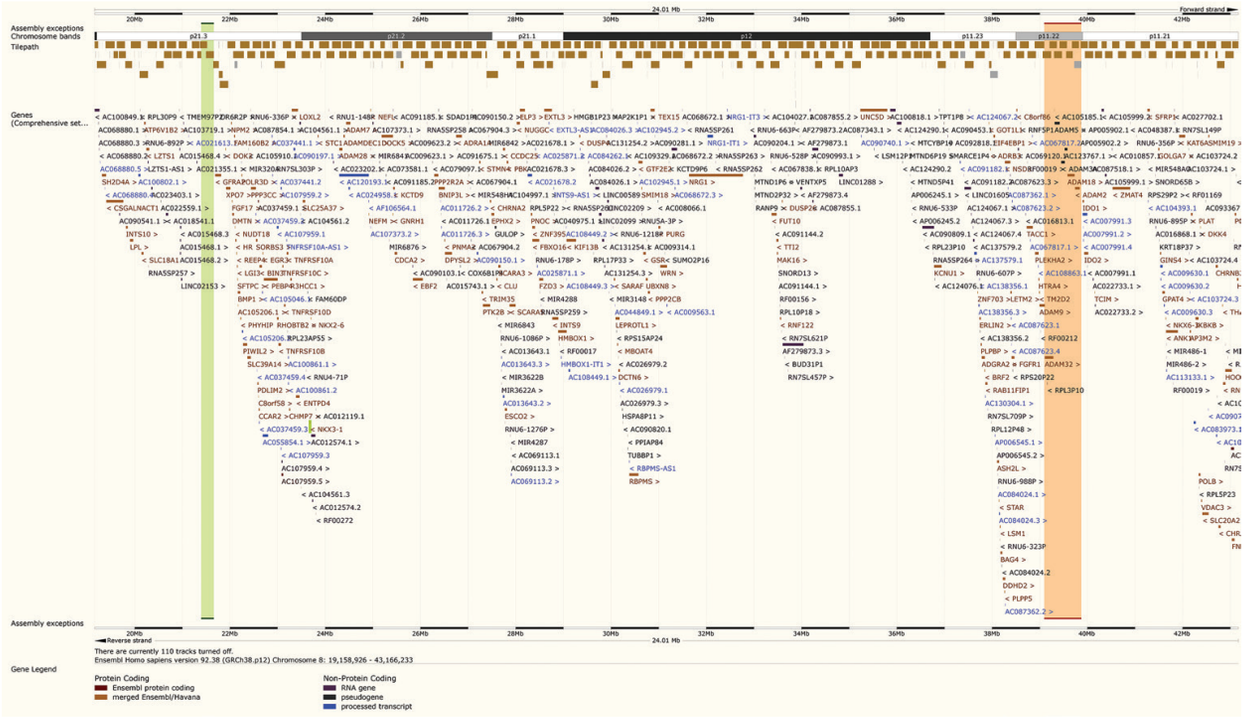

Figure 1. Some of the important genes located in 8p11-8p21 which are deleted up to 50–70% of prostate cancer (from http://www.ensembl.org).

(8–64 MB), and (5) extensive (71–132 MB), all were flanked by low copy repetitive (LCR) sequences [20]. All types had some gains of 3q21.1-3q29 and deletions at 8p, RB1, TP53 and TMPRSS2-ERG and ones with large interstitial deletion had worse prognosis [20]. Although PTEN deletions seem to affect aneuploidy through PIK3/Akt pathway, some other factors act directly. To give a sample, NKX3.1 binds to androgen receptor at the ERG gene breakpoint and inhibits the recombination of TMPRSS2 and ERG gene loci. Loss of NKX3.1 favors error-prone nonhomologous end-joining (NHEJ), further increasing TMPRSS2-ERG fusions [21]. Interestingly, intrinsic mechanism of the repair of DNA double-strand breaks (DSBs) driven by BRD4, itself may mediate the formation of oncogenic gene rearrangements by engaging the NHEJ pathway [22]. BRD4 belongs to the bromodomain and extra-terminal (BET) family of chromatin reader proteins that bind acetylated histones. These findings further outline importance of de novo alterations occurring synchronously are important for carcinogenesis together with error-prone intrinsic DNA repair mechanisms.

Again, the deletion of 16q23-q24 which is one of the most frequent genetic aberrations is associated with poor prognostic factors like advanced tumor stage, high Gleason grade, accelerated cell proliferation lymph node metastases and positive surgical margin [7, 23, 24]. Having ERG fusions were associated with higher incidence of 16q deletions [7, 23, 24]. Also, deletion of chromosome 13q occurs up to 50% of prostate cancer and its importance lies in the fact that this region contains RB transcriptional corepressor 1 gene which an important negative regulator of the cell cycle and the first tumor suppressor gene found [25, 26]. As well, deletion of three loci between 13q14.2 and 13q14.3 is associated with early biochemical relapse [27].

Other than structural chromosomal aberrations like aneuploidy, translocation, etc. epigenetics is another issue considered in carcinogenesis. The term "field cancerization" which had been suggested for head and neck cancers for the first time, refers to multifocal presence of genetic aberrations necessary for malignant transformation in a given tissue [28].

This term is also valid for prostate cancer, as cancerous tissues are multifocal with varying Gleason scores and preneoplastic tissues like high grade prostatic intraepithelial neoplasia (HGPIN) are detected closer to cancerous tissues [29]. This is further confirmed by methylation studies [30–35]. In a study comparing methylation status of GSTP1, MGMT, p14/ARF, p16/CDKN2A, RASSF1A, APC, TIMP3, S100A2 and CRBP1 genes among prostate cancer, HGPIN and BPH tissues, methylation was increased significantly from BPH to HGPIN and to prostate cancer [30]. Quantitative methylation specific PCR study of radical prostatectomy specimens, methylation of some genes like APC, RARb2 and RASSF1A were continuous in the histopathologically normal tissue around the cancerous tissue, forming a methylation halo up to 3 mm [31]. Another study including microarray study of methylation of large numbers of genes, the length of the halo was detected to be up to 10 mm [32].

3. Microenvironment

Prostatic stromal microenvironment is important for normal organogenesis as well as supporting carcinogenesis and the survival of the cancer cells [36, 37]. However, the exact pathways and stroma-tumoral interactions are poorly understood and still needed to be further clarified.

Cultured fibroblasts from regions close to prostate cancer cells were shown to induce tumor progression of initiated nontumorigenic epithelial cells both in an in vivo tissue recombination system and in an in vitro coculture system [38, 39]. Prostatic carcinoma-associated fibroblasts secrete SDF-1 which activates Akt pathway in the via the TGF-beta-regulated CXCR4 [40]. That is, TGF-beta promotes tumor formation although it has primarily growth-inhibitory action [40]. Marked reactive stroma is associated with poor prognosis in clinically localized prostate cancer and microarray gene expression analysis detected higher expression of 544 genes and lower expression of 606 genes in the reactive stroma, all of which have various functions like neurogenesis, axon genesis and DNA damage repair pathways [41]. In a recent study evaluating the nuclear and mitochondrial DNA integrity of prostate cancer cells, prostate cancer-associated stroma detected copy-neutral diploid genome with only rare and small somatic copy-number aberrations in contrast to several small somatic copy-number aberrations in prostate cancer cells [42]. This indicates, that above-mentioned gene expression changes in prostate cancer-adjacent stroma seem to be not related to frequent or recurrent genomic alterations in the tumor microenvironment [42].

Also, metabolic status of the prostatic stromal microenvironment has been suggested to influence the tumorigenic potential of the tumor epithelial compartment [43]. As well, it has been shown that the loss of the signaling adapter, p62, in stromal cells triggered an inflammatory response, activating cancer-associated fibroblasts which promotes tumor formation in vitro

and in vivo. Loss of p62 resulted in lower mTORC1 activity and deregulation of metabolic pathways related to the inflammation [44].

One interesting study, chronic bacterial inflammation with inoculated *Escherichia coli* bacteria induced focal prostatic glandular atypia/ prostatic intraepithelial neoplasia in male C3H/HeOuJ mice, suggesting a link between inflammation and prostatic neoplasia [45].

4. Sustaining proliferative signaling

To keep normal tissue architecture and function normal cells need to control proliferative signaling. However, in cancer cells, proliferative signaling is sustained to keep their growth. This is accomplished by either increased paracrine stimulation or excessive response to hormones by altered receptor matching or deregulated pathways. Insulin has been shown to activate insulin activated the insulin receptor (INSR) in case of inhibition of the IGF1 receptor (IGF1R) [46]. Mitochondrial redox signaling by p66Shc-ROS pathway has been shown to promote androgen-induced prostate cancer cell proliferation. As well, dihydrotestosterone was shown to increase the translocation of p66Shc into mitochondria and its interaction with cytochrome c [47]. The phosphatidylinositol 3′-kinase (PI3K) pathway has been suggested to be a dominant growth factor-activated cell survival pathway in prostate carcinoma cells. Apoptosis induced by PI3K inhibition has been shown to be reduced by either dihydrotestosterone or ErbB1 activating ligands which are epidermal growth factor, transforming growth factor alpha, and heparin-binding EGF-like growth factor [48]. Smad1 acts as a substrate for MAPKs and plays a central role in transmitting signals from the pathways of bone morphogenetic proteins. Deregulation of the pathways of bone morphogenetic proteins and activation of the ERK/MAP kinase (MAPK) pathway by growth factors was suggested to promote the development and progression of prostate cancer [49].

5. Evading growth suppressors and resisting cell death

In general sense, cancer cells need to gain new capabilities to suppress or bypass cell cycle checkpoints that negatively regulate the cell proliferation and promote apoptosis. Chromosome 17p includes an important gene, TP53 which encodes a tumor suppressor protein, p53, containing transcriptional activation, DNA binding, and oligomerization domains and it functions in cellular stresses to induce cell cycle arrest, apoptosis, senescence, DNA repair, or changes in metabolism. Deletion of chromosome 17p occurs mainly in advanced stages of prostate cancer and metastatic prostate cancer rather that early invasive prostate cancer [50–52]. BCL2 gene located in 18q21.33, encodes an integral outer mitochondrial membrane protein which blocks apoptosis. Its overexpression occurs in advanced, hormone-refractory disease [53].

Functional loss of CDKN1B which maps to 12p13.1 is prevalent in prostate cancer [54]. It inhibits cyclin-dependent kinase (CDK), sharing similarity with another inhibitor CDKN1A/p21. The encoded protein prevents the activation of cyclin E-CDK2 or cyclin D-CDK4 complexes,

in this way it controls the cell cycle progression at G1 stage. It is degraded through CDK dependent phosphorylation and subsequent ubiquitination by SCF complexes, permitting cellular transition from quiescence to the proliferative state. Its inactivation in prostate cancer is done by expression loss or increased degradation by abnormal phosphorylation and ubiquitinylating, rather than being mutated [55, 56].

Cyclin dependent kinase inhibitor 2A (CDKN2A) located in 9p21.3 encodes three alternatively spliced variants two of which encode structurally related isoforms functioning as inhibitors of CDK4 kinase and one variant functioning as stabilizer of the tumor suppressor protein p53. It is also rarely mutated in early prostate cancer, mainly mutated in advanced disease [57].

6. Enabling replicative immortality

Telomeres are located at the ends of eukaryotic linear chromosomes to protect chromosomes from end-to-end fusions and protect against the loss of terminal DNA during cell division [58]. Telomerase which is a ribonucleoprotein polymerase, maintains telomere length during cell divisions by addition of the telomere repeat TTAGGG [59]. Therefore, telomerase is also important for the maintenance of chromosomal stability and cellular immortality. The enzyme consists of a protein component with reverse transcriptase activity, telomerase reverse transcriptase (TERT) for adding telomeric DNA repeats onto chromosome ends and an RNA component (TERC) for adding telomeric DNA repeats onto chromosome ends [60, 61] Telomerase activity was detected in prostate cancer and high-grade prostatic intraepithelial neoplasia [62, 63]. Both TERT and TERC activities are important in telomere maintenance. Knockdown of TERC by siRNA has been shown to reduce proliferation of prostate cancer cells and increased TERC expression which is regulated by MYC, was detected in prostate cancer [64]. In benign prostatic hyperplasia, PIN and prostate cancer, high levels of telomere dysfunction were detected, and it was suggested that telomere dysfunction may play a role in carcinogenesis through genomic instability [65].

7. Inducing angiogenesis

As in any kind of tumoral tissue, tissue needs more blood supply as it grows uncontrolled. Therefore, cancer cells need to regulate pathways to induce angiogenesis. In prostate cancer related angiogenesis, ps20 which is a TGF-beta1-induced regulator of angiogenesis, has been suggested to promote endothelial cell migration and/or pericyte stabilization of newly formed vascular structures [66]. As well, stromal expression of connective tissue growth factor also promotes angiogenesis and therefore prostate cancer progression. Expression of CTGF in tumor-reactive stroma has been shown to induce increased micro-vessel density. CTGF which is also a downstream mediator of TGF-beta1 seem to be another important regulator of angiogenesis in the tumor-reactive stromal microenvironment [67].

8. Activating invasion and metastasis

Epithelial cancers progress to higher pathological grades of malignancy carcinomas and become locally invasive and metastatic to distant locations. This is termed as epithelial to mesenchymal cell transition during which the, the associated cancer cells alter their shape, their attachment to other cells and the extracellular matrix.

Abnormal increased expression of the mitochondrial ribosomal protein S18-2 has been shown to induce epithelial to mesenchymal cell transition in prostate cancer through the TWIST2/E-cadherin signaling and induce CXCR4-mediated migration of prostate cancer cells [68]. MiRNALet-7a has been shown to induce invasion of prostate cancer cells and induce migration by stimulating epithelial-mesenchymal transition through CCR7/MAPK pathway [69]. Interestingly, inactivation of the androgen receptor resulted in lower expression of a transcriptional repressor (SAM pointed domain-containing ETS transcription factor, SPDEF) of CCL2, which mediates epithelial to mesenchymal cell transition of the prostate cancer cells. That may explain progression to metastatic stage in a subset of castration resistant prostate cancer [70].

9. Reprogramming of energy metabolism

It has been shown that energy metabolism of early prostate cancers mainly depends on lipids and other energetic molecules for energy production and not on aerobic respiration or aerobic glycolysis (Warburg effect) [71]. Initially defined by Otto Warburg, the Warburg effect defines increased rate of glucose uptake, lactate production in proliferating cells in the presence of oxygen and fully functioning mitochondria [72]. The Warburg effect is the first defined energy metabolism of cancer cells energy [72]. However, in prostate cancer that is not the matter, as prostate cancer cells do not have increased glucose uptake except advanced stage disease [73].

In the advanced stages, reduced mtDNA content is a critical step in the metabolism restructuring for cancer cell progression. As, MtDNA depleted prostate cancer cells exhibit Warburg effect [74]. Reduced microRNA-132 (miR-132) expression was suggested to cause metabolic switch in prostate cancer cells by inhibiting Glut1 expression which results increased rate of lactate formation, cellular glucose uptake and the rapid growth of the cancer cells [75].

10. Evading immune destruction

The immune system acts a barrier to tumor formation and progression. The role of immune system is clear when increased malignancies in transplant patients is considered. In patients with renal transplants, genitourinary malignancies are the third most common malignancy after skin malignancies and lymphoproliferative disorders [76–78].

Cancer cell transfer extracellular vesicle-mediated estrogen receptor-binding fragment-associated antigen 9 (EBAG9) to their microenvironment promoting self-immune escape and further progression. EBAG9 suppresses T-cell infiltration into tumor in vivo and limits T-cell cytotoxicity [79]. Interestingly, the adaptive immune system was suggested to promote de novo prostate carcinogenesis in a human c-Myc transgenic mouse model [80]. Recently, tumoral exosome-immune cell cross-talk has been suggested [81]. Prostate-cancer-derived exosomal prostaglandin E2 (PGE2) was suggested to result impaired CD8+ T cell response immunosuppression via exosomal regulation of dendritic cell function [81]. Exosomal PGE2 triggered potently the expression of CD73, an ecto-5-nucleotidase responsible for AMP to adenosine hydrolysis, on dendritic cells. CD73 induction of dendritic cell resulted in an ATP-dependent inhibition of TNFα- and IL-12-production [81].

11. Conclusions

Above briefly mentioned properties of prostate cancer cells and related genes, genetic pathways and their interactions have still no specific clinical use in prostate cancer management.

Yet, we are too far to understand the exact genetic mechanisms underlying prostate carcinogenesis. But, it is sure that as we progress in further researches we will be more surprised to find out unknown interactions of supposed to be well known genetic mechanism.

Conflict of interest

There is conflict of interest.

Author details

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References

[1] Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000;**100**(1):57-70

[2] Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. Cell. 2011;**144**(5): 646-674

[3] Cancer Genome Atlas Research N. The molecular taxonomy of primary prostate cancer. Cell. 2015;**163**(4):1011-1025

[4] Kunimi K, Bergerheim US, Larsson IL, Ekman P, Collins VP. Allelotyping of human prostatic adenocarcinoma. Genomics. 1991;**11**(3):530-536

[5] Bergerheim US, Kunimi K, Collins VP, Ekman P. Deletion mapping of chromosomes 8, 10, and 16 in human prostatic carcinoma. Genes, Chromosomes & Cancer. 1991;**3**(3):215-220

[6] Saramaki OR, Porkka KP, Vessella RL, Visakorpi T. Genetic aberrations in prostate cancer by microarray analysis. International Journal of Cancer. 2006;**119**(6):1322-1329

[7] Osman I, Scher H, Dalbagni G, Reuter V, Zhang ZF, Cordon-Cardo C. Chromosome 16 in primary prostate cancer: A microsatellite analysis. International Journal of Cancer. 1997;**71**(4):580-584

[8] Chang M, Tsuchiya K, Batchelor RH, Rabinovitch PS, Kulander BG, Haggitt RC, et al. Deletion mapping of chromosome 8p in colorectal carcinoma and dysplasia arising in ulcerative colitis, prostatic carcinoma, and malignant fibrous histiocytomas. The American Journal of Pathology. 1994;**144**(1):1-6

[9] Matsuyama H, Pan Y, Skoog L, Tribukait B, Naito K, Ekman P, et al. Deletion mapping of chromosome 8p in prostate cancer by fluorescence in situ hybridization. Oncogene. 1994;**9**(10):3071-3076

[10] Bowen C, Bubendorf L, Voeller HJ, Slack R, Willi N, Sauter G, et al. Loss of NKX3.1 expression in human prostate cancers correlates with tumor progression. Cancer Research. 2000;**60**(21):6111-6115

[11] He WW, Sciavolino PJ, Wing J, Augustus M, Hudson P, Meissner PS, 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

[12] Ornstein DK, Cinquanta M, Weiler S, Duray PH, Emmert-Buck MR, Vocke CD, et al. Expression studies and mutational analysis of the androgen regulated homeobox gene NKX3.1 in benign and malignant prostate epithelium. The Journal of Urology. 2001;**165**(4):1329-1334

[13] Abdulkadir SA, Magee JA, Peters TJ, Kaleem Z, Naughton CK, Humphrey PA, et al. Conditional loss of Nkx3.1 in adult mice induces prostatic intraepithelial neoplasia. Molecular and Cellular Biology. 2002;**22**(5):1495-1503

[14] Damaschke NA, Yang B, Bhusari S, Avilla M, Zhong W, Blute ML Jr, et al. Loss of Igf2 gene imprinting in murine prostate promotes widespread neoplastic growth. Cancer Research. 2017;**77**(19):5236-5247

[15] Yoshimoto M, Ding K, Sweet JM, Ludkovski O, Trottier G, Song KS, et al. PTEN losses exhibit heterogeneity in multifocal prostatic adenocarcinoma and are associated with higher Gleason grade. Modern Pathology. 2013;**26**(3):435-447

[16] Phin S, Moore MW, Cotter PD. Genomic rearrangements of PTEN in prostate cancer. Frontiers in Oncology. 2013;**3**:240

[17] Murphy SJ, Karnes RJ, Kosari F, Castellar BE, Kipp BR, Johnson SH, et al. Integrated analysis of the genomic instability of PTEN in clinically insignificant and significant prostate cancer. Modern Pathology. 2016;**29**(2):143-156

[18] Gao T, Mei Y, Sun H, Nie Z, Liu X, Wang S. The association of phosphatase and tensin homolog (PTEN) deletion and prostate cancer risk: A meta-analysis. Biomedicine & Pharmacotherapy. 2016;**83**:114-121

[19] Bismar TA, Yoshimoto M, Vollmer RT, Duan Q, Firszt M, Corcos J, et al. PTEN genomic deletion is an early event associated with ERG gene rearrangements in prostate cancer. BJU International. 2011;**107**(3):477-485

[20] Vidotto T, Tiezzi DG, Squire JA. Distinct subtypes of genomic PTEN deletion size influence the landscape of aneuploidy and outcome in prostate cancer. Molecular Cytogenetics. 2018;**11**:1

[21] Bowen C, Zheng T, Gelmann EP. NKX3.1 suppresses TMPRSS2-ERG gene rearrangement and mediates repair of androgen receptor-induced DNA damage. Cancer Research. 2015;**75**(13):2686-2698

[22] Li X, Baek G, Ramanand SG, Sharp A, Gao Y, Yuan W, et al. BRD4 promotes DNA repair and mediates the formation of TMPRSS2-ERG gene rearrangements in prostate cancer. Cell Reports. 2018;**22**(3):796-808

[23] Kluth M, Runte F, Barow P, Omari J, Abdelaziz ZM, Paustian L, et al. Concurrent deletion of 16q23 and PTEN is an independent prognostic feature in prostate cancer. International Journal of Cancer. 2015;**137**(10):2354-2363

[24] Harkonen P, Kyllonen AP, Nordling S, Vihko P. Loss of heterozygosity in chromosomal region 16q24.3 associated with progression of prostate cancer. The Prostate. 2005;**62**(3):267-274

[25] Cooney KA, Wetzel JC, Merajver SD, Macoska JA, Singleton TP, Wojno KJ. Distinct regions of allelic loss on 13q in prostate cancer. Cancer Research. 1996;**56**(5):1142-1145

[26] Li C, Larsson C, Futreal A, Lancaster J, Phelan C, Aspenblad U, et al. Identification of two distinct deleted regions on chromosome 13 in prostate cancer. Oncogene. 1998;**16**(4):481-487

[27] Brookman-Amissah N, Nariculam J, Freeman A, Willamson M, Kirby RS, Masters JR, et al. Allelic imbalance at 13q14.2 approximately q14.3 in localized prostate cancer is associated with early biochemical relapse. Cancer Genetics and Cytogenetics. 2007;**179**(2):118-126

[28] Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. Cancer. 1953;**6**(5):963-968

[29] Qian J, Wollan P, Bostwick DG. The extent and multicentricity of high-grade prostatic intraepithelial neoplasia in clinically localized prostatic adenocarcinoma. Human Pathology. 1997;**28**(2):143-148

[30] Jeronimo C, Henrique R, Hoque MO, Mambo E, Ribeiro FR, Varzim G, et al. A quantitative promoter methylation profile of prostate cancer. Clinical Cancer Research. 2004;**10**(24):8472-8478

[31] Mehrotra J, Varde S, Wang H, Chiu H, Vargo J, Gray K, et al. Quantitative, spatial resolution of the epigenetic field effect in prostate cancer. The Prostate. 2008;**68**(2):152-160

[32] Yang B, Bhusari S, Kueck J, Weeratunga P, Wagner J, Leverson G, et al. Methylation profiling defines an extensive field defect in histologically normal prostate tissues associated with prostate cancer. Neoplasia. 2013;**15**(4):399-408

[33] Van Neste L, Bigley J, Toll A, Otto G, Clark J, Delree P, et al. A tissue biopsy-based epigenetic multiplex PCR assay for prostate cancer detection. BMC Urology. 2012;**12**:16

[34] Wojno KJ, Costa FJ, Cornell RJ, Small JD, Pasin E, Van Criekinge W, et al. Reduced rate of repeated prostate biopsies observed in ConfirmMDx clinical utility field study. American Health & Drug Benefits. 2014;**7**(3):129-134

[35] Stewart GD, Van Neste L, Delvenne P, Delree P, Delga A, McNeill SA, et al. Clinical utility of an epigenetic assay to detect occult prostate cancer in histopathologically negative biopsies: Results of the MATLOC study. The Journal of Urology. 2013;**189**(3):1110-1116

[36] Li H, Fan X, Houghton J. Tumor microenvironment: The role of the tumor stroma in cancer. Journal of Cellular Biochemistry. 2007;**101**(4):805-815

[37] Taylor RA, Risbridger GP. Prostatic tumor stroma: A key player in cancer progression. Current Cancer Drug Targets. 2008;**8**(6):490-497

[38] Olumi AF, Dazin P, Tlsty TD. A novel coculture technique demonstrates that normal human prostatic fibroblasts contribute to tumor formation of LNCaP cells by retarding cell death. Cancer Research. 1998;**58**(20):4525-4530

[39] Olumi AF, Grossfeld GD, Hayward SW, Carroll PR, Tlsty TD, Cunha GR. Carcinoma-associated fibroblasts direct tumor progression of initiated human prostatic epithelium. Cancer Research. 1999;**59**(19):5002-5011

[40] Ao M, Franco OE, Park D, Raman D, Williams K, Hayward SW. Cross-talk between paracrine-acting cytokine and chemokine pathways promotes malignancy in benign human prostatic epithelium. Cancer Research. 2007;**67**(9):4244-4253

[41] Dakhova O, Ozen M, Creighton CJ, Li R, Ayala G, Rowley D, et al. Global gene expression analysis of reactive stroma in prostate cancer. Clinical Cancer Research. 2009;**15**(12):3979-3989

[42] Bianchi-Frias D, Basom R, Delrow JJ, Coleman IM, Dakhova O, Qu X, et al. Cells comprising the prostate cancer microenvironment lack recurrent clonal somatic genomic aberrations. Molecular Cancer Research. 2016;**14**(4):374-384

[43] Lisanti MP, Martinez-Outschoorn UE, Sotgia F. Oncogenes induce the cancer-associated fibroblast phenotype: Metabolic symbiosis and "fibroblast addiction" are new therapeutic targets for drug discovery. Cell Cycle. 2013;**12**(17):2723-2732

[44] Valencia T, Kim JY, Abu-Baker S, Moscat-Pardos J, Ahn CS, Reina-Campos M, et al. Metabolic reprogramming of stromal fibroblasts through p62-mTORC1 signaling promotes inflammation and tumorigenesis. Cancer Cell. 2014;**26**(1):121-135

[45] Elkahwaji JE, Hauke RJ, Brawner CM. Chronic bacterial inflammation induces prostatic intraepithelial neoplasia in mouse prostate. British Journal of Cancer. 2009;**101**(10): 1740-1748

[46] Weinstein D, Sarfstein R, Laron Z, Werner H. Insulin receptor compensates for IGF1R inhibition and directly induces mitogenic activity in prostate cancer cells. Endocr Connect. 2014;**3**(1):24-35

[47] Veeramani S, Yuan TC, Lin FF, Lin MF. Mitochondrial redox signaling by p66Shc is involved in regulating androgenic growth stimulation of human prostate cancer cells. Oncogene. 2008;**27**(37):5057-5068

[48] Lin J, Adam RM, Santiestevan E, Freeman MR. The phosphatidylinositol 3′-kinase pathway is a dominant growth factor-activated cell survival pathway in LNCaP human prostate carcinoma cells. Cancer Research. 1999;**59**(12):2891-2897

[49] Qiu T, Grizzle WE, Oelschlager DK, Shen X, Cao X. Control of prostate cell growth: BMP antagonizes androgen mitogenic activity with incorporation of MAPK signals in Smad1. The EMBO Journal. 2007;**26**(2):346-357

[50] Saric T, Brkanac Z, Troyer DA, Padalecki SS, Sarosdy M, Williams K, et al. Genetic pattern of prostate cancer progression. International Journal of Cancer. 1999;**81**(2):219-224

[51] Brooks JD, Bova GS, Ewing CM, Piantadosi S, Carter BS, Robinson JC, et al. An uncertain role for p53 gene alterations in human prostate cancers. Cancer Research. 1996;**56**(16):3814-3822

[52] Voeller HJ, Sugars LY, Pretlow T, Gelmann EP. p53 oncogene mutations in human prostate cancer specimens. The Journal of Urology. 1994;**151**(2):492-495

[53] McDonnell TJ, Navone NM, Troncoso P, Pisters LL, Conti C, von Eschenbach AC, et al. Expression of bcl-2 oncoprotein and p53 protein accumulation in bone marrow metastases of androgen independent prostate cancer. The Journal of Urology. 1997;**157**(2):569-574

[54] Macri E, Loda M. Role of p27 in prostate carcinogenesis. Cancer Metastasis Reviews. 1998;**17**(4):337-344

[55] Cordon-Cardo C, Koff A, Drobnjak M, Capodieci P, Osman I, Millard SS, et al. Distinct altered patterns of p27KIP1 gene expression in benign prostatic hyperplasia and prostatic carcinoma. Journal of the National Cancer Institute. 1998;**90**(17):1284-1291

[56] Iacopino F, Angelucci C, Lama G, Zelano G, La Torre G, D'Addessi A, et al. Apoptosis-related gene expression in benign prostatic hyperplasia and prostate carcinoma. Anticancer Research. 2006;**26**(3A):1849-1854

[57] Gu K, Mes-Masson AM, Gauthier J, Saad F. Analysis of the p16 tumor suppressor gene in early-stage prostate cancer. Molecular Carcinogenesis. 1998;**21**(3):164-170

[58] Blackburn EH. Telomeres and telomerase: The means to the end (Nobel lecture). Angewandte Chemie (International Ed. in English). 2010;**49**(41):7405-7421

[59] Greider CW, Blackburn EH. Identification of a specific telomere terminal transferase activity in Tetrahymena extracts. Cell. 1985;**43**(2 Pt 1):405-413

[60] Feng J, Funk WD, Wang SS, Weinrich SL, Avilion AA, Chiu CP, et al. The RNA component of human telomerase. Science. 1995;**269**(5228):1236-1241

[61] Greider CW, Blackburn EH. A telomeric sequence in the RNA of Tetrahymena telomerase required for telomere repeat synthesis. Nature. 1989;**337**(6205):331-337

[62] Lin Y, Uemura H, Fujinami K, Hosaka M, Harada M, Kubota Y. Telomerase activity in primary prostate cancer. The Journal of Urology. 1997;**157**(3):1161-1165

[63] Zhang W, Kapusta LR, Slingerland JM, Klotz LH. Telomerase activity in prostate cancer, prostatic intraepithelial neoplasia, and benign prostatic epithelium. Cancer Research. 1998;**58**(4):619-621

[64] Baena-Del Valle JA, Zheng Q, Esopi DM, Rubenstein M, Hubbard GK, Moncaliano MC, et al. MYC drives overexpression of telomerase RNA (hTR/TERC) in prostate cancer. The Journal of Pathology. 2018;**244**(1):11-24

[65] Tu L, Huda N, Grimes BR, Slee RB, Bates AM, Cheng L, et al. Widespread telomere instability in prostatic lesions. Molecular Carcinogenesis. 2016;**55**(5):842-852

[66] McAlhany SJ, Ressler SJ, Larsen M, Tuxhorn JA, Yang F, Dang TD, et al. Promotion of angiogenesis by ps20 in the differential reactive stroma prostate cancer xenograft model. Cancer Research. 2003;**63**(18):5859-5865

[67] Yang F, Tuxhorn JA, Ressler SJ, McAlhany SJ, Dang TD, Rowley DR. Stromal expression of connective tissue growth factor promotes angiogenesis and prostate cancer tumorigenesis. Cancer Research. 2005;**65**(19):8887-8895

[68] Mushtaq M, Jensen L, Davidsson S, Grygoruk OV, Andren O, Kashuba V, et al. The MRPS18-2 protein levels correlate with prostate tumor progression and it induces CXCR4-dependent migration of cancer cells. Scientific Reports. 2018;**8**(1):2268

[69] Tang G, Du R, Tang Z, Kuang Y. MiRNALet-7a mediates prostate cancer PC-3 cell invasion, migration by inducing epithelial-mesenchymal transition through CCR7/MAPK pathway. Journal of Cellular Biochemistry. 2018;**119**(4):3725-3731

[70] Tsai YC, Chen WY, Abou-Kheir W, Zeng T, Yin JJ, Bahmad H, et al. Androgen deprivation therapy-induced epithelial-mesenchymal transition of prostate cancer through downregulating SPDEF and activating CCL2. Biochimica et Biophysica Acta. 2018;**1864**:1717-1727

[71] Sadeghi RN, Karami-Tehrani F, Salami S. Targeting prostate cancer cell metabolism: Impact of hexokinase and CPT-1 enzymes. Tumour Biology. 2015;**36**(4):2893-2905

[72] Warburg O, Wind F, Negelein E. The metabolism of tumors in the body. The Journal of General Physiology. 1927;**8**(6):519-530

[73] Dueregger A, Schopf B, Eder T, Hofer J, Gnaiger E, Aufinger A, et al. Differential utilization of dietary fatty acids in benign and malignant cells of the prostate. PLoS One. 2015;**10**(8):e0135704

[74] Li X, Zhong Y, Lu J, Axcrona K, Eide L, Syljuasen RG, et al. MtDNA depleted PC3 cells exhibit Warburg effect and cancer stem cell features. Oncotarget. 2016;**7**(26):40297-40313

[75] Qu W, Ding SM, Cao G, Wang SJ, Zheng XH, Li GH. miR-132 mediates a metabolic shift in prostate cancer cells by targeting Glut1. FEBS Open Bio. 2016;**6**(7):735-741

[76] Penn I. The changing pattern of posttransplant malignancies. Transplantation Proceedings. 1991;**23**(1 Pt 2):1101-1103

[77] Penn I. Posttransplant malignancies. Transplantation Proceedings. 1999;**31**(1-2):1260-1262

[78] Villeneuve PJ, Schaubel DE, Fenton SS, Shepherd FA, Jiang Y, Mao Y. Cancer incidence among Canadian kidney transplant recipients. American Journal of Transplantation. 2007;**7**(4):941-948

[79] Miyazaki T, Ikeda K, Sato W, Horie-Inoue K, Inoue S. Extracellular vesicle-mediated EBAG9 transfer from cancer cells to tumor microenvironment promotes immune escape and tumor progression. Oncogene. 2018;**7**(1):7

[80] Melis MHM, Nevedomskaya E, van Burgsteden J, Cioni B, van Zeeburg HJT, Song JY, et al. The adaptive immune system promotes initiation of prostate carcinogenesis in a human c-Myc transgenic mouse model. Oncotarget. 2017;**8**(55):93867-93877

[81] Salimu J, Webber J, Gurney M, Al-Taei S, Clayton A, Tabi Z. Dominant immunosuppression of dendritic cell function by prostate-cancer-derived exosomes. Journal of Extracellular Vesicles. 2017;**6**(1):1368823