Molecular Pathways of Prostate Carcinoma

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Öz

Prostat Karsinomunun Moleküler Yolakları

Prostat kanseri, dünyada hızla artan insidans oranlarına sahip en yaygın kanser türlerinden biridir. Prostat kanseri insidansı ve mortalite oranları farklı popülasyonlarda büyük ölçüde değişkendir. Prostat kanseri, tümör baskılayıcı genlerin spesifik genom sekanslarında delesyon ve onkogen aktivasyonu ile ilişkili spesifik kromozomal bölgelerdeki değişiklikler gibi çoklu genetik modifikasyonları içerir. Prostat kanseri yol açan kalıtsal değişikliklerin bir veya daha fazla spesifik genetik özellik ile ilişkili olup olmadığını belirlemek zordur. Prostat karsinogenezi çok karmaşık olup hala mekanizmaları olarak açıklanmamıştır. Eğer prostat karsinogenezini daha iyi anlayabilirsek bu hastalar için hedefe yönelik tedavi de bulabiliriz. Bu nedenle biz burada prostat karsinomunda yer alan büyük genetik ve epigenetik değişikliklerden bahsetmek istedik.
Anahtar Kelimeler: Prostat Karsinomu, Moleküler Yolaklar, Tedavi, Epigenetik

Abstract

Molecular Pathways of Prostate Carcinoma

Prostate cancer is one of the most common types of cancer with rapidly growing incidence rates in the world. The incidence and mortality rates of prostate cancer are widely variable in different populations. The prostate cancer includes multiple genetic modifications such as deletion in specific genome sequences of tumor-suppressor genes and alterations in specific chromosomal sites associated with oncogene activation. It is difficult to determine whether the hereditary changes leading to prostate cancer are associated with one or more specific genetic features. Prostate carcinogenesis is complex and has not been fully explained. If we can better understand prostate carcinogenesis, we can also find targeted therapy. Therefore, we talked about the major genetic and epigenetic changes involved in prostate carcinoma.
Keywords: Prostate Carcinoma, Molecular Pathways, Treatment, Epigenetic

INTRODUCTION

Prostate cancer (PCa) is one of the most common types of cancer with rapidly growing incidence rates in the world. The incidence and mortality rates of PCa are widely variable in different populations; however, it is the major type of non-cutaneous cancers in men in most parts of the world. When we look at the data of 2018, 1 276 106 new prostate cancer patients were detected. Moreover, according to the latest data, in 2018, 358 989 people died from prostate cancer (1). Although prostate carcinoma is so common, its treatment has not been fully established. Prostate carcinogenesis is complex and has not been fully explained. If we can better understand prostate carcinogenesis, we can also find targeted therapy. Therefore, we talked about the major genetic and epigenetic changes involved in prostate carcinoma.

The importance of pathology in the treatment of prostate cancer

Early diagnosis and treatment have been made available for the patients since the use of serum prostate-specific antigen (PSA) levels were implemented in the clinical practice (2). However; after observing that a considerable number of patients were treated unnecessarily, active surveillance has been introduced as a strategy to follow up these patients (3). Various sets of criteria have been proposed so far to define the patient population, in whom the active treatment strategies could be deferred without compromising the chances of cure. Today, different active surveillance criteria are implemented for the clinical practice in individual medical centers, providing the grounds to discuss patient outcomes. The most commonly used criteria to define an insignificant PCa were developed by Epstein et al (4). This set of criteria includes the

diagnosis of a stage T1c disease clinically, the presence of a PSA density of <0.15 ng/ml, the absence of Gleason pattern 4 or 5, detection of tumor tissue in less than 3-core biopsy samples, and the presence of a less than 50% presence of tumor tissue per each core biopsy sample. Furthermore, patient preference for the treatment options is critical, too. Another point to consider is the low chances for the cure in metastasized PCa while the chances for the cure exist in the localized disease. Therefore, the debate over these issues still goes on (5). As mentioned above, one of the criteria to determine whether to include the patient in active surveillance is the diagnosis made based on the results of the prostate needle biopsy. It should be noted that the results of the prostate needle biopsy examination are limited to the presence of the tumor in the biopsy specimen. Only the Gleason score of the tumor tissue in the needle biopsy specimen will be reported. However, the examination of the resection material may reveal the presence of other tumor tissue areas with high Gleason scores. Therefore; based on these findings, active surveillance decision should not only be made by taking the risk groups into consideration, but the decision process should include the evaluation of the general health condition of the patient, his life expectations, and personal choices as well.

Molecular changes in prostate carcinoma

Cancer can simply be defined as uncontrolled cell proliferation. Besides the uncontrolled cell division, cancer cells are also characterized by the absence of the need for stimulation to divide, loss of contact inhibition, insensitivity to growth-inhibitory signals, the ability to evade apoptosis, the ability to stimulate angiogenesis, and the capacity for metastasis (6). Similar to other types of cancer, prostate cancer develops when the glandular epithelium undergoes pre-neoplastic changes prostatic intraepithelial neoplasia (PIN) and transforms into invasive carcinoma due to genetic and epigenetic modifications. Like the other types of cancer, the factors involved in the carcinogenesis of the prostate include multiple genetic modifications such as deletion in specific genome sequences of tumor-suppressor genes and alterations in specific chromosomal sites associated with oncogene activation. It is difficult to determine whether the hereditary changes leading to PCa are associated with one or more specific genetic features. Some of the somatic changes are genetic in carcinogenesis, occurring as point mutations, amplifications, deletions, and translocations. Remaining changes are epigenetic, and the major ones include alterations in the chromatin structure and deoxycytidine methylation patterns (7).

Functional androgen receptor (AR) and androgen hormones are essential for the normal development of the prostate, its secretory functions, and luminal cell survival. AR is not a classical oncogene. All genetic and epigenetic changes, occurring in the conversion process of the epithelial cells to tumor cells, induce angiogenesis, stimulate the cell growth, and inhibit apoptosis. All these processes occur via AR signaling and their occurrence is impossible without AR signaling (8). The main molecular pathways and genes effective in normal prostate development and carcinogenesis are summarized in Table-1.

Table 1. Molecular pathways and genes in prostate development and carcinogenesis

Normal development	**AR** **NKX3.1** **FGF7** **FGF10** **TGFB1** **HoxD13**
Initiation and progression to carcinoma	**PTEN** **RB** **MYC** **FGFs** **E-cadherin** **P27 loss** **NKX3.1 loss** **6p loss** **13q loss**
Advanced carcinoma and metastasis	**AR** **p53** **Bcl2** **PTEN loss** **PI3K/Akt activation** **Notch pathway** **AR mutation** **AR LBD mutation** **AR-dependent fusion oncoproteins** **AR amplification**

(FGF: Fibroblast Growth Factor, TGFB: Transforming growth factor beta, LBD: Ligand-Binding Domain)

"Erythroblast Transformation-specific-related Gene" (ERG) and "ETS translocation variant 1" (ETV1) are two members of the ETS transcription family. They are over expressed both in the primary and metastatic PCa. These genes are activated by TMPRSS2, which is the prostate-specific cell surface serine protease gene, to be involved in the synthesis of androgen-responsive oncoproteins (9). An analysis study described repeating gene fusions across the 5'-noncoding region of the androgen-responsive TMPRSS2

gene and the DNA-binding transcription factors of the ETS family in approximately half of the prostate carcinomas and in 20% of HPINs. These fusions support the over expression of the members of the ETS transcription factor family, including ERG, ETV1, and ETV4. The TMPRSS2-ERG fusion accounts for 90% of the fusions in prostate cancer. Immunohistochemical staining with ERG is a substitute for ERG rearrangement as a reliable marker. A recent study has suggested that the ERG protein expression at the time of diagnosis can identify the patients with a high risk of disease progression during active surveillance (10,11).

PI3K/AKT/mTOR signaling cascade directly or indirectly acts on the regulating mechanisms of growth, proliferation, and survival of the cell (12). PI3K is a complex family, comprising three classes and containing numerous subunits and isoforms. mTOR protein is a serine/threonine kinase, which controls angiogenesis and progression of the cell cycle (13).

Following the activation of PI3K, the synthesis of PIP3 in the internal cell membrane interacts directly with the PH domain of AKT, leading to its induction. Another PH domain, which is called 3-phosphoinositide-dependent protein kinase-1 (PDK1) and which contains serine/threonine kinase, phosphorylates AKT. This phosphorylation is necessary for the activation of AKT. AKT activation stimulates the growth, multiplication, and survival of the cell consequently (13). The increase in the levels of the active forms of Phosphatidylinositol 3-kinase (PI3K) and AKT stimulates tumoral angiogenesis. PI3K and serine/threonine kinase AKT activate mTOR in mammal cells via two different mechanisms, namely by direct phosphorylation and TSC2 inactivation. Activated mTOR (p-mTOR) stimulates protein synthesis and regulates the cell cycle by means of the downstream effectors P70S6K and 4E-BP1. Activated P70S6K (p-P70S6K) stimulates protein synthesis, too. Phosphorylation of 4E-BP1 by p-mTOR leads to the activation of the cap-dependent translation of the nuclear mRNA. Therefore, the activation of the AKT/mTOR/4E-BP1/P70S6K pathway causes general protein translation. Studies in the literature have demonstrated that the inhibitors of mTOR may be effective by its growth-inhibiting and anti-angiogenic features in some types of cancer (14).

"Phosphatase and tensin homolog" gene (PTEN) is located on chromosome 10q24. It regulates apoptosis by inhibiting the "phosphatidylinositol 3-kinase/protein kinase B" (P13K/AKT) signaling pathway. PTEN deletion results in the aggravation of cell proliferation. Deletion of PTEN or the activation of the PI3K/AKT pathway is frequently detected in invasive and metastatic human prostate cancers. When deletion of PTEN co-exists with other pathways, which affect tumor induction or aggravation of tumor aggression minimally, they may act in collaboration. An example for these processes can be the increased rate of tumor progression and progression to fatal prostate cancer in the presence of a deletion in PTEN and in P53, which is a tumor suppressor. A PTEN deletion is observed in variable rates ranging from 5% to 27% in non-metastatic prostate tumors; however, the rates increase to 30-60% in metastatic prostate cancers (15). PTEN deletion models in mice mimic several aspects of human prostate cancer, including the disease progression, expression of the molecular markers, and similar gene expression profiles. Studies using these models have demonstrated that PTEN deletion is involved in the induction of prostate cancer (16,17).

Notch signal pathway is critically important in the normal development of the prostate gland. Notch signals are essential for the specialization of the prostate cells at their specific location during the embryonic and postnatal growth and development (18). Several studies investigating the relationship between prostate cancer and the Notch signal pathway found out that Notch signal pathway is involved in the carcinogenesis of the prostate, increasing the rate of cell proliferation, inhibiting apoptosis, enhancing the migration and invasion of the cells, and acting on the metastatic processes (18-20). As the spectrum of progression widens in the prostate cancer tissue, the expression of the members of the Notch signal pathway have been found out to increase, too (20). Prostate cancer often metastasizes to the bone, lymph nodes, and the brain (21,22). Expression of the members of the Notch pathway is observed to increase in metastatic prostatic carcinoma cell lines.

There are several tumor suppressor genes located on chromosome 8p. Among them, the "prostate-specific homeobox gene" (NKX3.1) is located at 8p21.2. The product of the NKX3.1 gene suppresses PSA gene expression by binding the DNA. This gene is found in androgen-sensitive cells and it is involved in the development of normal prostate tissue. Deletion of the NKX3.1 gene may explain the high levels of PSA expression in prostate cancer (23).

p27 is the tumor suppressor gene located on the chromosome 12p12-3 and it is involved in the carcinogenesis of the prostate. It codes "cyclin-dependent kinase inhibitor 1B" (CDKN1b). The level of p27 is especially low in aggressive prostate cancers with poor prognosis. p27 works in correlation with PTEN, CDKN1b, and NKX3.1. p53 mutations have been demonstrated in advanced stage prostate cancers, in patients with metastases to bones, and in androgen-independent tumors at a rate of 42% (24). The retinoblastoma gene (RB) is located on chromosome 13q and is one of the genes regulating apoptosis. Its presence is reported in patients with prostate carcinoma. Like RB, some of the other cyclin-dependent kinase inhibitor proteins, which are p15, p16, and p21 work in correlation as the regulators of tumor suppression and the cell cycle. They

are observed more commonly in the advanced stage prostate cancers or metastatic tumors compared to the primary cancer cases (25).

"Prostate stem cell antigen" (PSCA) is expressed in 80% of PCa and in high-grade PIN cases. The elevation of the PSCA levels has been found to be correlated with high Gleason scores, advanced disease stages, and androgen treatment (26).

MYC amplification is found at variable rates in PCa. Also, N-MYC amplification and overexpression are common in neuroendocrine prostate cancer (27).

The RAS gene is located on the short arm of chromosome 12. RAS signaling is of critical importance in normal cells for division, differentiation, and survival. RAS is the most frequently mutated oncogene in cancer and various types of RAS have been identified in several cancer types (28). The rates of RAS mutations are variable in PCa from 5% in the Western populations to 26% in the Japanese population (29).

Bcl-2 is an androgen-independent protein in the antiapoptotic protein family. It does not exist in the normal prostate tissue, but its expression has been demonstrated in half of the PCa cases.

Numerous mRNA expressions of STAMP2 (six transmembrane protein of prostate 2) were found in PCa. STAMP2 is regulated by androgen in androgen receptor positive PCa cells but it is not expressed in the androgen negative cells (30).

For the epigenetic changes involved in the development of prostate cancer, numerous types of genes have been identified as potentially beneficial future molecular biomarkers. Among them, "glutathione-S-transferase P1" (GSTP1) is an important one identified in more than 90% of prostate cancers (31). GSTP-1 gene codes the "glutathione-S-transferase" (GST) enzymes. GSTs constitute the enzyme family, which detoxify the oxidants. The function of GSTP1 is lost when hypermethylation of the "cytosine-guanine" (CpG) island of GSTP1 occurs. This deletion renders the prostate cells susceptible to carcinogenesis, which is affected by inflammation and dietary factors.

Despite the fact that the heritability of PCa is the highest among all other major types of cancer, the efforts to define hereditary prostate cancer syndromes and to identify the responsible genes remain to be limited compared to other cancer types (32,33). These efforts in identifying the responsible genes involved in the development of PCa mainly concentrate on European studies examining family-based linkages of the hereditary prostate cancer. The series of probably associated genes include HPC1 (1q24-25), PCAP (1q42-43), HPCX (Xq27-28), CAPB (1q36), HPC20 (20q13), and HOXB13 among others (34,35). The series of identified or confirmed loci in non-European linkage studies include 12q24, 1q24-25, 2p16, 2p21, and 1p36 at 22 and AA21 in the Japanese population (32,33). In addition, linkage signals have been reported to exist in AA pedigrees at 2p21, 11q22, 17p11, 22q12, and Xq21 (36). Interestingly, studies evaluating most of these specifically identified, confirmed, or signal-detected loci suggest the possibility of common hereditary origins in developing PCa across the populations based on the validation of these findings in various ethnic and geographic groups of individuals. Although genetic tests for predicting hereditary prostate cancer still awaits to be introduced to clinical practice along with the development of genetic structure-based recommendations to reduce the potential harm of the disease as it is the case in other major types of cancer; some implications for treatment has recently been introduced after identifying the associations of inherited mutations of BRCA2 with aggressive PCa. The validation of some of the loci with the use of multiple methods in both the family linkage studies and genome-wide association studies (GWASs) in more than one ethnic and racial groups of individuals and the estimated discrepancies in the results of this two group of studies suggest that the involvement of these genes in the etiology of prostate cancer may signify the presence of a spectrum (37,38).

Attempts for the transcriptional and proteomic profiling of PCa continued to grow rapidly during the last decade but male urogenital cancers still remain to be the most challenging type of cancer. The absence of an effective treatment regimen for PCa patients, especially for castration-resistant PCa, and the rapid development of treatment resistance in patients led investigator efforts to find out the carcinogenesis-associated processes in the prostate. These studies mainly aim to find a method to predict the prognosis in PCa and to establish targeted treatments.

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