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# Key Genes in Prostate Cancer Progression: Role of MDM2, PTEN, and TMPRSS2-ERG Fusions

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Additional information is available at the end of the chapter

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## Abstract

In recent years, multiple genes or their protein products have been linked to initiation and progression of prostate cancer. Such genes include TMPRSS2, ERG, PTEN, and MDM2. This chapter discusses the pathological roles as well as the potential diagnostic and therapeutic applications of these genes that are highly expressed in prostate cancer when compared to other cancer types. The presence of these genes and related defects are linked to growth, progression, metastasis, invasiveness and resistance in prostate cancers. While knowledge related to TMPRSS2, ERG, and PTEN have been accumulating in the last two decades, the prometastatic role of MDM2 has been emerging in the last few years and revealing important functions related to prostate cancer progression.

**Keywords:** prostate cancer, TMPRSS2-ERG, PTEN, MDM2

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## 1. Introduction

Prostate cancer (PCa) is a long latency tumor that occurs in males that are typically aged 50 years and older. Globally, more than 1.1 million cases of prostate cancer were recorded in 2012, accounting for around 8% of all new cancer cases and 15% in men [1]. In 2015, an estimated 220,800 men will be diagnosed with PCa in the United States and an estimated 27,540 men will die due to the disease making this malignancy the second leading cause of cancer-related death in men [2]. In addition, African-American (AA) men have the highest incidence and mortality from PCa when compared to other races [2]. The pathophysiology of prostate cancer is not fully elucidated, but it is well established that this dreadful disease is primarily initiated by cellular proliferation within pre-existing ducts and glands, which is

referred to as Prostatic intraepithelial neoplasia (PIN). The PIN eventually progresses to invasive prostate cancer [3]. Clinical manifestations of the disease are variable and based on the transport by blood or the lymphatic system to metastatic sites and the effects of localized tumor growth. Localized prostate cancer is typically curable with targeted local therapy such as radical prostatectomy or radiation therapy. In metastatic prostate cancer, one of the successful strategies of treatment is surgical or chemical castration leading to androgen deprivation therapy (ADT) [4]. Unfortunately, approximately 33% of patients develop resistance to these treatments with the eventual increases in the number of androgens, prostate specific antigen (PSA), and circulating tumor cells (CTCs), leading to the more progressive and metastatic castration resistant prostate cancer (CRPC) [5]. The poor prognosis associated with metastatic prostate cancers is attributable in part to the highly heterogeneous nature of the cancer cells, which provides a significant hurdle for treatment of the disease [6]. Multiple genomic alterations underlie the clinical heterogeneity of prostate cancer and such aberrations include, point mutations, microsatellite variations, and chromosomal alterations such as translocations, insertions, duplications, fusions, and deletions [6, 7]. Therefore, there is a heightened interest in understanding the role of these genetic changes in prostate cancer development and progression.

## 2. Key genes in prostate cancer progression

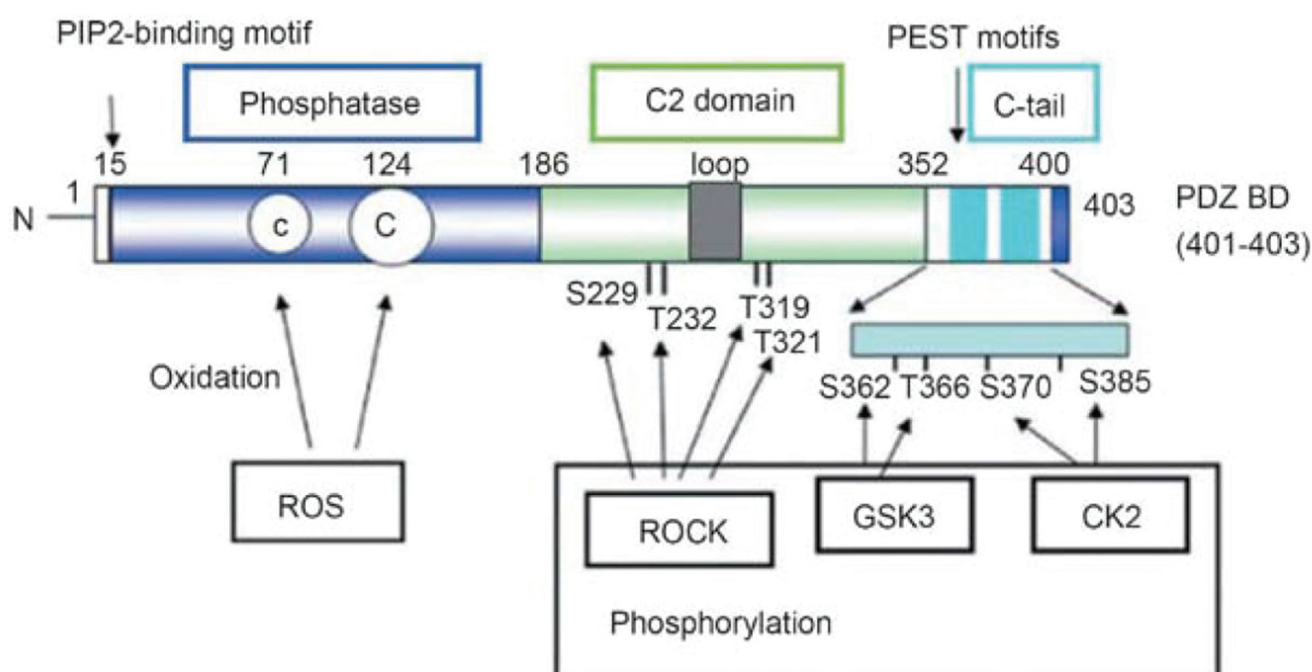
In the past decade, several genes associated with prostate cancer have been identified. Four such genes: the ETS-related gene (ERG), The Transmembrane Protease Serine 2 (TMPRSS2), Mouse double minute 2 homolog (MDM2), and Phosphatase and tensin homolog (PTEN) have gained recognition for their high specificity of expression in prostatic carcinomas.

### 2.1. Prostate cancer and PTEN

PTEN is a protein coding gene that encodes for phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase. It contains a tensin-like domain in addition to a catalytic domain similar to that of the dual specificity protein tyrosine phosphatases. PTEN is one of the most commonly mutated tumor suppressor genes in human prostate cancer. Interestingly, many aspects of PTEN expression and function, including transcriptional and post-transcriptional regulation, post-translational modifications, and protein-protein interactions have been shown to be altered in human prostate cancer. PTEN is a non-redundant phosphatase that directly interferes with the phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway and thereby controls several processes that are important in the homeostasis of cell survival and a multitude of cellular functions, which includes growth, proliferation, metabolism, migration, and cellular architecture [8]. PTEN removes the phosphate from the D3 position of phosphatidylinositol-3,4,5-triphosphate (PIP3), a product of PI3K, thus, can lead to inhibition of downstream AKT activation in normal conditions. However, when PTEN is mutated there is sustained activation of AKT that can lead to cell proliferation, angiogenesis and other related events. AKT exists in three isoforms, namely AKT1, AKT2, and AKT3, which are typically activated by the

phosphorylation at two specific sites: Thr308 by PDK1 [9] and Ser473 by the mammalian target of rapamycin complex 2 (mTORC2) [10]. Activated AKT can drive cell survival, proliferation, growth, angiogenesis, and metabolism by phosphorylating downstream signaling proteins, which include inhibitory phosphorylation of GSK3, FOXO, BAD, p21, p27, and PGC I and activating phosphorylation of mTORC I mammalian target of rapamycin complex I (mTORC I), IKK- $\beta$ , MDM2, ENTPD5, SREBP1C, AS160, and SKP2, which eventually leads to cell cycle progression and proliferation [10, 11]. Inhibition of GSK3 $\beta$  has been shown to specifically prevent the degradation of cyclin D1 and  $\beta$ -catenin, which can further support G1 to S phase transition in different types of cancers including prostate cancers [11, 12]. Activation of AKT also helps to evade apoptosis directly by phosphorylation of the pro-apoptotic protein BAD [13]. Hence, re-expression of wild-type *PTEN* in *PTEN* null prostate cancer cell lines can lead to the initiation of apoptosis and regression of tumors [14]. In addition, AKT directly activates the mTOR pathway by phosphorylating TSC2, which dismantles the TSC1/TSC2 complex that keeps the Rheb in an inhibited state. Once released from the TSC1/TSC2 inhibition, the Rheb can stimulate the phosphotransferase activity of mTORC1 and phosphorylate the S6 kinase (S6K) and 4E-binding protein (4EBP1), which in turn initiates cap-dependent protein translation [15, 16]. Therefore, as a consequence of *PTEN* loss in prostate cancers, PI3K/AKT/mTOR pathway activation can strongly lead to enhanced translation of mRNAs involved in cell growth and proliferation.

The *PTEN* gene is comprised of nine exons and totally codes for 403 amino acids [17]. The substrate binding site of *PTEN* is in the C2 domain, which can bind to the phospholipid membranes. The C2 domain also contains a signature motif HCXXGXXR that is typically found in the protein tyrosine phosphatases (PTPs) and in the dual specific protein phosphatases (DPPs). In addition, there is a short phosphatidylinositol-4,5-bisphosphate (PIP2) binding domain (PDB) on the N terminus, a motif on the C-terminal tail that interacts with PDZ-BD domain-containing proteins, and regulates protein stability and two PEST domains containing proline (P), glutamic acid (E), serine (S), and threonine (T) amino acids, which acts as a signal peptide that is also involved in the stability and degradation of *PTEN* [18]. When PIP2 binds to the PDB domain of *PTEN* it produces a conformational change in the protein leading to allosteric activation of substrate binding site for attracting the substrates for de-phosphorylation [19]. In addition to the allosteric activation, the positive charge of the substrate binding pocket of *PTEN*'s is also essential for accommodating larger substrates such as phosphoinositides. The phosphatase domain of *PTEN* is a evolutionarily conserved domain that harbors nearly 40% of its cancer-associated mutations, and the most common mutations are C124S mutation, which abolishes both lipid binding and protein phosphatase activity, and the G129E mutation that destroys the lipid phosphatase activity [20–22]. However, some of the important *PTEN* tumorigenic mutations occur on the C2 domain also, confirm the importance of the structural integrity of the C terminus in maintaining *PTEN* activity and protein stability [23, 24] (**Figure 1**). In prostate cancer, *PTEN* loss most commonly results from a somatic mutation generated through copy number loss rather than point mutation [25, 26], however, recent exome sequencing has identified several recurrent mutations also in the *PTEN* gene [27, 28].



**Figure 1.** Different domains of PTEN and the phosphorylation sites. (Obtained from: Cell Res. 2008; 18: 807–816.)

### 2.1.1. PTEN loss combined with alterations in inflammatory pathway regulators

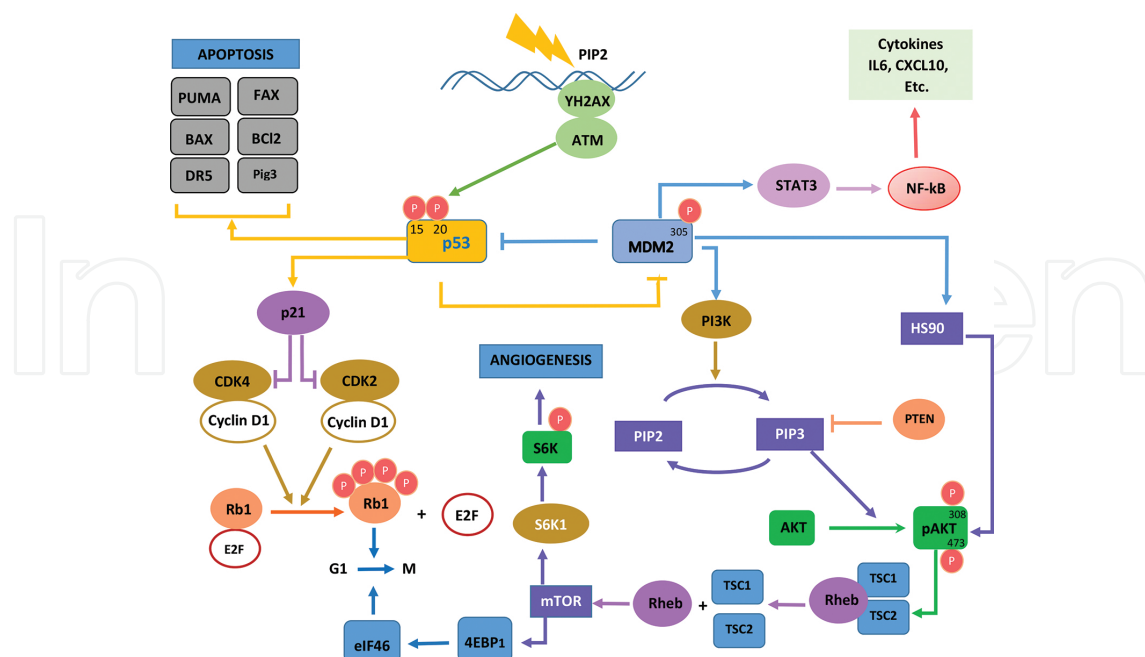
Various lines of evidence suggest that chronic inflammation is a closely associated event in the tumorigenic mechanisms of prostate cancer [29, 30] and to the several mutations that are causing this disease. A cytokine that is most commonly associated with tumor growth, proliferation, and angiogenesis in many cancers and also the most frequently found inflammatory mediator in prostate cancer is IL-6 [31]. When expressed at high levels, in addition to imposing the inflammatory functions, a strong correlation between the circulating levels of IL-6 and advancement in the stages of prostate cancer, therapeutic resistance, and as a result an overall poor prognosis has been well established until now [32]. Although one of the most important consequences of IL-6 expression is the stimulation of the JAK/STAT3 pathway [33], phosphorylation of STAT3 at Ser727 and activation of its function by the PI3K-AKT pathway cannot be ruled out completely because of the impact PTEN mutations can produce on this pathway [34]. Such activation of STAT3 can also lead to metastatic behavior of prostate cancer cells in both *in vitro* and *in vivo* conditions, through stimulation of angiogenesis and suppression of antitumor immune responses [35]. Many inflammatory cytokines and chemokines promote tumor progression by converging on and stimulating the IKK2/NF- $\kappa$ B signaling axis [36]. In addition to the above-mentioned mechanisms, constitutive activation of NF- $\kappa$ B has been correlated well with disease progression in prostate cancer [37], and therefore inhibition of NF- $\kappa$ B activity in prostate cancers can suppress angiogenesis and subsequent tumor invasion and metastasis by downregulating downstream targets such as VEGF and MMP9 [38]. In this context, it was determined using a mouse model that a constitutively active version of IKK2 alone is insufficient for promoting prostate tumorigenesis; however, in combination



with even heterozygous loss of *PTEN*, *IKK2* activation can lead to an increase in tumor size, accompanied by increased inflammation [39]. Thus, earlier studies clearly demonstrate that the inflammatory cytokines secreted from the stromal microenvironment of the prostate cells can cooperate with *PTEN* loss to drive epithelial prostate tumor towards an invasive disease. Interestingly, recent studies have clearly indicated a greater role for the *MDM2* oncogene in the progression of prostate cancer by impacting *PI3K/AKT* and *NF-κB* pathways [40, 41].

## 2.2. MDM2 and prostate cancer

Alterations in the *TP53* gene is one of the most commonly detected gene defects in a wide range of cancers; however, alterations of this gene is believed to be of low frequency in prostate cancer [42], and their clinical significance is also not fully investigated. On the contrary, the *MDM2* gene seems to be amplified in a significant fraction of prostate cancers, and overexpression of *MDM2* protein without amplification is also observed as an alternate mechanism of *p53* inactivation in these cancers [43, 44]. It has been widely reported that *p21/WAF1* gene expression could very well serve as an indicator of *p53* activity because *p21/WAF1* is under the transcriptional control of *p53* and therefore can be severely impacted when *MDM2* is overexpressed. However, the *MDM2* gene itself is under the transcriptional control of *p53*, which creates an auto-regulatory feedback loop in many cancer types (Figure 2) [45]. An interesting fact that was revealed through mutation analysis of various cancer samples is that, in prostate cancers, alterations in the *TP53* gene seem to be uncommon, and therefore the clinical significance of *TP53* gene mutation has not been fully investigated for prostate cancers. Another important limitation of studies related to *TP53* gene defect in prostate cancer is that, in many cases their focus was confined to the analysis of *p53* gene alterations without exploring other



**Figure 2.** The pro-angiogenesis, apoptosis, cytokine release, and cell cycle pathways that are impacted by *MDM2* expression.

possible mechanisms that might regulate its functions. For example, though the *MDM2* gene is amplified in a variety of tumors, *MDM2* overexpression without amplification seems to be a common mechanism of p53 inactivation in certain cancers. As it was mentioned earlier in this section, it has been well established that *p21/WAF1* gene expression can serve as a good indicator of p53 activity, because *p21/WAF1* expression is under the transcriptional control of p53, and consequently indicate any related abnormality. However, several studies have analyzed the patterns of p53 expression and identified a correlation with *MDM2* and p21 in prostate cancer patients. Results have confirmed a close association between levels of these markers and clinico-pathological parameters of poor outcome, including time to relapse and proliferative index. In addition, overexpression of *MDM2* has been found to be associated with lack of response to chemoradiotherapy in oesophageal cancer and has been shown to exhibit androgen independence in prostate cancer cell lines [46, 47]. Thus, *MDM2* overexpression was significantly associated with advanced stage prostate cancer (PCa) [48], a finding confirmed by several investigators [49, 50] validating the importance of *MDM2* expression in prostate cancers. Recent studies have also shown that *MDM2* expression enhances the angiogenic potential and proliferative capacity of PCa cells [51] and negatively impacts the effects of radiation and chemotherapy [52]. Thus, it is predictable that expression of *MDM2* may play an important role, at least in part, in stimulating the aggressive nature of PCa in African-American (AA) patients. Recently, a single nucleotide polymorphism (SNP) referred as SNP309 was found at position 309 in the P2 promoter region of *MDM2* gene. This T > G polymorphism (rs22789744) which is located in the intronic portion of the promoter was shown to increase the binding affinity of the transcriptional activator Sp1, and increase the expression of *MDM2* protein levels [53]. During the transcriptional activation of *MDM2* gene, both the androgen receptor (AR) and estrogen receptors (ER) have been shown to form complexes with Sp1 and act as co-regulators and cause increase in protein expression [54, 55]. In addition, studies in ER-positive tumors such as breast and ovarian cancer have shown strong correlation between younger age of disease onset and the presence of *MDM2* SNP309 G allele [56, 57]. Interestingly, in the ovarian cancer patients, the age of onset in women with high level expression of ER and the presence of SNP309 G allele was 8 years earlier than those without the SNP309 G allele. Similarly, in a cohort of breast cancer patients with the G/G SNP309 genotype the age of onset was 7 years earlier than the patients with the T/T genotype. Furthermore, *MDM2* SNP309 G allele displayed early-onset of soft-tissue sarcoma, diffuse large B-cell lymphoma, colorectal cancer, and non-small cell lung cancer in premenopausal women with active estrogen signaling than the cohorts without the SNP309 polymorphism [58–61]. Hence, it is believed that SNP309 G allele found at the *MDM2* promoter region in AA patients may be responsible for the aggressive phenotype and early onset of their prostate cancers (48). Indeed, this appears to be one of the first studies of *MDM2* SNP309 showing the implication of this particular polymorphism to the racial differences in the clinic-pathologic presentation of the prostate cancer. Additionally, the above mentioned study is the first report that is closely correlating SNP309 genotype to *MDM2* protein expression in a group of prostate cancer patients and showing its close correlation with tumor progression. Thus, several aspects of *MDM2* expression and the gene polymorphisms seem to specifically impact the nature and progression of prostate cancers.

### 2.2.1. MDM2 and cytokine expression

In addition to being the trigger for developing cancers, MDM2 expression seems to be responsible for several events that promote cancer aggressiveness [48]. Increased expression of VEGF in cancer cells, which are positive for MDM2, is a well-established phenomenon that occurs through elevation of HIF-1 $\alpha$  even during the absence of hypoxia in the tumor microenvironment [51]. In addition, many reports in the literature confirm that MDM2 overexpression could lead to activation of STAT3 and NF- $\kappa$ B pathways and cause elevation of cytokines that in-turn can stimulate cancer progression. One of the unique biological functions of MDM2 is its ability to induce sterile tissue inflammation, which is a major element of non-infectious tissue injury that occurs following exposure to toxins or reperfusion following ischemia. For example, an acute post-ischemic kidney injury that started as a sterile inflammatory response was reversed using the MDM2 blockade with nutlin-3 [62]. This effect was found to be totally independent of p53 that was observed in a p53-deficient mice. Also, MDM2 blockade effectively suppressed the post-ischemic induction of pro-inflammatory cytokines and chemokines as well as the infiltration of leukocytes to the site of injury. Following these observations, the mechanism underlying MDM2-mediated inflammation was identified under *in vitro* conditions showing that MDM2 could act as a co-factor for NF- $\kappa$ B binding to its gene promoter binding sites [62]. This was actually confirmed by the electromobility shift assay in p53-deficient mouse embryonic fibroblasts using lipopolysaccharide (LPS) stimulation [62]. This observation is similar to several other reports which confirm that MDM2 blockade with nutlin-3 could effectively suppresses LPS-induced lung inflammation through interference of NF- $\kappa$ B DNA binding in neutrophils; however this effect of nutlin-3 was dependent on the presence of intact p53 [62]. Similar to the activation of NF- $\kappa$ B pathway, MDM2 might release other cytokines like Interleukins (IL's) and support growth and progression of cancer.

### 2.3. TMPRSS2 and ERG fusions in prostate cancer

TMPRSS2 is an androgen regulated prostate-specific protein that is encoded in humans by the TMPRSS2 gene [63]. It is a 492 amino acid type II transmembrane serine protease (70 KDa) that is expressed at the cell surface in order to regulate cell-cell and cell-matrix interactions [64]. The serine protease gene family, play crucial roles in different physiological and pathological processes such as digestion, blood coagulation, remodeling of tissues, invasion of tumor cells, inflammatory responses, and apoptosis. The TMPRSS2 protein contains a Serine protease domain (aa 255-492) with three catalytic residues of histidine, aspartate, and serine, respectively, a Scavenger receptor cysteine-rich domain (SRDR, aa 149-242), an LDL receptor class A (LDLRA, aa 113-148) domain and a predicted transmembrane domain (aa 84-106) [65].

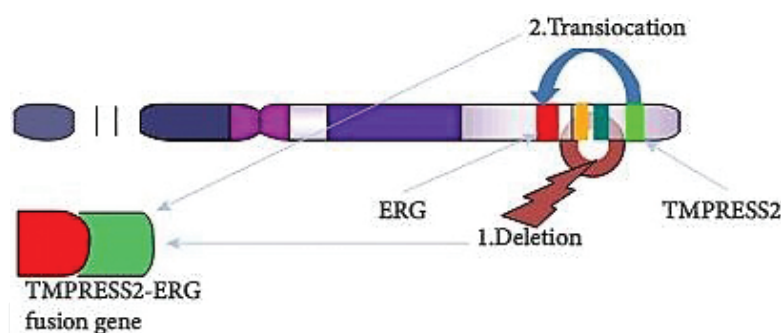
ERG is a member of the erythroblastosis virus E26 (ETS) oncogene family. There are over 20 ETS transcription factor family members, but ERG is the ETS transcription factor primarily involved in prostate cancer gene fusions [66]. The ERG protein interacts with ETS members as well as other transcription factors through its protein-protein interacting domain to regulate



transcriptional activity of several downstream target genes that are crucial for DNA damage, cell invasion and proliferation, epithelial to mesenchymal transformation (EMT) as well as cellular differentiation and epigenetic control [66–68].

TMPRSS2 is expressed in normal and neoplastic prostate tissue and is strongly induced by androgens in androgen-sensitive prostate cell lines [65]. A major milestone in PCa research was the identification of recurrent fusions between TMPRSS2 and ERG [63]. TMPRSS2-ERG is fused in PCa through deletion of genomic DNA via a homogeneous deletion site between ERG and TMPRSS2 on chromosome 21q22.2 or through translocation or both [69–71]. These rearrangements (**Figure 1**) result in the formation of a TMPRSS2-ERG fusion transcript and the overexpression of ERG [63]. The TMPRSS2 and ERG genes are both located on the same chromosome (21q) and the distance between the TMPRSS2 and ERG oncogene is relatively short at 3 mega bases (MB) (**Figure 3**). This short distance has been suggested to account for the higher frequency of TMPRSS2: ERG fusions in prostate cancer [69, 73].

TMPRSS2-ERG fusion occurs early in prostate carcinogenesis at the transition between benign and prostatic intraepithelial neoplasia (PIN). Approximately 50% of PCas from prostate-specific antigen (PSA) screened surgical cohorts are TMPRSS2-ERG fusion-positive, and >90% of PCas over-expressing ERG harbor TMPRSS2-ERG fusions [74]. Over eight isoforms of the TMPRSS2-ERG fusion transcript have been identified with varying levels of expression in different PCa samples [75]. The most frequently found TMPRSS2-ERG fusion in PCa is the deletion between the 5' UTR end of TMPRSS2 exon 1 and 5' end of ERG exon 4 [76].



**Figure 3.** Mechanism of TMPRSS2-ERG fusion (chromosome 21). (1) Large deletion of intervening genetic region between ERG and TMPRSS2 genes (most common). (2) Translocation of TMPRSS2 and ERG genes. Reproduced with permission from the copyright holder: Hossain [72].

### 2.3.1. Consequences of TMPRSS2-ERG fusion in prostate cancer

TMPRSS2 is an androgen-responsive gene and AR regulated expression of the TMPRSS2-ERG fusion gene plays an early role in prostate cancer development and progression as its presence is required for prostate cancer initiation in ETS positive tumors [74]. The fusion results in the modulation of transcriptional patterns and cellular pathways causing the development of prostatic intraepithelial neoplasia (PIN) [77]. In particular, gene expression profiling has linked a deregulation of WNT and TGF- $\beta$ /BMP signaling in

fusion-positive prostate tumors [78]. It has also been shown in transgenic mice that overexpression of ERG as a result of TMPRSS2: ERG fusion leads to the formation of murine PIN (mPIN) by 5–6 months of age [74, 79]. Several studies have also confirmed that the overexpression of ERG leads to prostate cell migration and invasion that correlates with increased tumor metastasis and negative patient outcome [79, 80]. The most prominent role of ERG that has been consistently shown is its ability to increase cell migration and invasion via abrogating prostate epithelial differentiation and inducing epithelial to mesenchymal transition and motility-associated genes such as MMPs [81].

PCa specimens containing the TMPRSS2-ERG rearrangement are also significantly enriched for the loss of tumor suppressor gene phosphatase and tensin homologue PTEN [77], and it is already well established that aberrant PTEN activity is associated with poor prognosis in PCa [82]. Further studies have confirmed that TMPRSS2-ERG rearrangement cooperates with PTEN loss to promote prostate cancer progression from high-grade prostatic intraepithelial neoplasia (PIN) to invasive adenocarcinoma [77, 83].

### *2.3.2. TMPRSS2-ERG fusions and ethnicity*

There are several studies evaluating the relationship between ethnicity and TMPRSS2-ERG expression in PCa. TMPRSS2-ERG gene fusion correlated with ethnicity in a multivariate analysis involving Caucasians [71], African-Americans, and Japanese men with PCa [71]. TMPRSS2-ERG gene fusion was present in 50% (21/42) of Caucasians, 31.3% (20/64) of African-Americans, and 15.9% (7/44) of Japanese patients. A subsequent study found that TMPRSS2-ERG gene fusions were identified in 48/112 tumors (42.9%) from a group of Caucasian men, while 28/105 tumors (26.7%;  $p = 0.015$ ) from African-American men were positive for the gene fusion [84]. Interestingly, Mosquera and colleagues recognized that the TMPRSS2-ERG fusion through deletion, which has been associated with worse prognosis, is more common in PCa of African-American patients [73].

### *2.3.3. Prognostic value of the TMPRSS2-ERG fusion gene*

The prognostic potential of TMPRSS2-ERG gene fusion is promising as it can be detected in urine, blood, and tissue using quantitative polymerase chain reaction [85, 86], Fluorescence in situ hybridization (FISH) [87], DNA sequencing, and Genechip [88]. This has significant applications toward understanding its role in PCa pathogenesis and developing novel diagnostics and targeted therapeutics. TMPRSS2 and TMPRSS2-ERG expression is decreased in response to ADT in primary PCa [89]. Interestingly, the ERG levels in TMPRSS2-ERG fusion-positive castration resistant prostate cancer CRPC are comparable with the levels in fusion gene-positive primary PC, and this confirms that TMPRSS2-ERG expression is reactivated by AR in CRPC [70]. These findings prove that restored AR receptor signaling contributes to the progression to CRPC in part through the TMPRSS2-ERG axis and highlights a therapeutic platform that can be explored in the management of CRPC. More recently, the TMPRSS2-ERG fusion has been linked to taxane resistance in preclinical models of castration-resistant prostate cancer, and TMPRSS2-ERG expression detection in the peripheral blood of metastatic castration-resistant prostate cancer patients correlates with docetaxel resistance [90]. Therefore, its

presence predicts resistance to docetaxel, and it may be useful to select treatment and to avoid possible toxicities in refractory patients.

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