Molecular Biology Underlying the Clinical Heterogeneity of Prostate Cancer

An Update

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• ***Context.***—**Recent studies have uncovered a number of possible mechanisms by which prostate cancers can become resistant to systemic androgen deprivation, most involving androgen-independent reactivation of the androgen receptor. Genome-wide expression analysis with microarrays has identified a wide array of genes that are differentially expressed in metastatic prostate cancers compared to primary nonrecurrent tumors. Recently, recurrent gene fusions between *TMPRSS2* and *ETS* family genes have been identified and extensively studied for their role in prostatic carcinoma.**

Objective.—**To review the recent developments in the molecular biology of prostate cancer, including those pertaining to the androgen receptor and the newly identified *TMPRSS2*-related translocations.**

Data Sources.—**Literature review and personal experience.**

Conclusions.—**Prostatic adenocarcinoma is a heterogeneous group of neoplasms with a broad spectrum of pathologic and molecular characteristics and clinical behaviors. Numerous mechanisms contribute to the development of resistance to androgen ablation therapy, resulting in ligand-independent reactivation of the androgen receptor, including amplification, mutation, phosphorylation, and activation of coreceptors. Multiple translocations of members of the *ETS* oncogene family are present in approximately half of clinically localized prostate cancers. *TMPRSS2:ERG* gene rearrangement appears to be an early event in prostate cancer and is not observed in benign or hyperplastic prostatic epithelium. Duplication of *TMPRSS2:ERG* appears to predict a worse prognosis. The relationship between *TMPRSS2:ERG* gene rearrangement and other morphologic and prognostic parameters of prostate cancer is still unclear.**

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Prostate cancer is the most common noncutaneous malignancy in men and the second most common cause of cancer deaths, accounting for 186 320 new annual cases and 28 660 deaths in America and an annual incidence of 679 023 cases and 221 002 deaths worldwide in 2008.[1,2] The highest incidence of prostate cancer is found in the United States, Canada, and Scandinavia, and the lowest in China and other parts of Asia.[3,4] Risk factors include advancing age, African American ethnicity, family history, and diet.[5–9] The increasingly widespread testing for serum levels of prostate-specific antigen (PSA) has allowed for the increasing detection of prostate cancers at earlier stages of development. As a result, prostatic adenocarcinoma has become a clinically heterogeneous entity, with some early carcinomas following an indolent clinical course, remaining confined to the prostate with little effect on overall lifespan, while other cases can lead to the development of lethal metastatic disease. Despite the recent advances in treatment modalities, surgical, radiation, and hormonal therapies for prostate cancer are not without complications, making the development of methods for distinguishing indolent cancers from their aggressive counterparts necessary to avoid excessive treatment that may lead to significant morbidity.[10] Furthermore, current methods of treating advanced metastatic disease often prove to be insufficient in the long-term. Recent research has therefore sought to identify new molecular pathways by which investigators can distinguish indolent prostate cancers from those that go on to pursue a more aggressive clinical course, as well as to discover new targets for the treatment of metastatic carcinomas.

Previous cytogenetic and molecular studies[11–21] had shown that prostatic adenocarcinomas tend to incur frequent and consistent losses of specific chromosomal loci, including chromosomes 8p, 10q, 13q, and 17p, and, less commonly, 6q, 7q, 16q, and 18q, as well as gains in chromosomes 7 and 8q. More recently, investigators compared the gene expression profiles of primary nonrecurrent prostatic adenocarcinomas and metastatic prostate cancers by using microarrays.[22] Genes that were more highly expressed in metastatic carcinomas included those involved in DNA synthesis and repair, mitosis, and cell cycle regulation, such as *RFC5*, *TOP2A*, *RFC4*, and *MAD2L1*, which have previously been shown to be highly expressed in proliferating cells.[23] Other differentially expressed genes

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included those involved in signal transduction, transcriptional regulation, chromatin modification, RNA processing, protein synthesis, posttranslational protein modification, cell adhesion, cell migration, cytoskeletal regulatory elements, extracellular matrix proteins, biosynthetic enzymes, and transport proteins.[22] Several unclassified genes with unknown functions were also found to be differentially expressed.[22]

PROSTATIC ADENOCARCINOMA RESISTANT TO ANDROGEN ABLATION THERAPY

Prostate cancer affects 1 of 9 men older than 65 years.[24] Age correlates with a decrease in the ratio of androgens to estrogens in men, suggesting that a physiologic change in hormonal status may contribute to the progression of preneoplastic lesions to adenocarcinoma.[25–27] Androgen ablation therapy is the most common systemic treatment for metastatic disease; it prevents testosterone production by the testes and thereby causes tumor regression during the short-term by depleting androgen-dependent carcinoma cells.[28,29] Androgen deprivation can be achieved surgically or by medical castration, which can be performed by the administration of estrogens and gonadotropin-releasing agonists and antagonists, and has been shown to be effective in treating advanced and metastatic disease in several large clinical trials.[30–33] However, most prostatic adenocarcinomas become refractory to androgen ablation.[34] Experiments with animal models of prostatic adenocarcinomas,[34,35] such as Dunning R-3327-H rat prostate carcinomas and the transgenic adenocarcinoma mouse prostate model, have shown that androgen therapy ultimately selects for androgen-independent carcinoma cells during the long-term, leading to the development of highly aggressive, androgen-resistant tumors. Despite this progression to more aggressive disease, it is still advised that patients with hormone-resistant cancers continue to receive androgen ablation therapy.[36]

Aberrant activation of the androgen receptor (AR) can result from gene amplification, mutation, phosphorylation, activation of coregulators, or androgen-independent activation. Most cases of prostatic carcinoma resistant to androgen ablation therapy demonstrate activation of AR by one of these mechanisms.[37–39] The AR gene is either mutated or amplified in 20% to 30% of androgen-resistant prostate carcinomas.[40–42] Further, 20% of hormone-resistant carcinomas contain gene amplifications as compared to just 2% of hormone-sensitive tumors, suggesting that aberrant activation in response to low levels of androgens or other ligands may underlie the progression to aggressive disease that is refractory to androgen ablation therapy.[43] Specific mutations, such as the T877A and H874Y substitutions, confer increased sensitivity to AR for steroid hormones such as progesterone, 17β-estradiol, or hydroxyflutamide in prostate cancer cell lines and xenografts.[44,45] Mutant AR containing the E231G substitution has also been shown to predispose transgenic mice to the development of prostatic intraepithelial neoplasia (PIN), adenocarcinoma, and metastases.[46] Experiments have shown that AR hyperactivity results in the formation of prostatic neoplasms: overexpression of AR leads to the development of focal PIN, whereas AR overexpression in LAPC-4 prostate cancer cells and xenografts results in a transition from androgen-sensitive disease to androgen-resistant cancer.[47,48] Phosphorylation of AR at different specific serine residues may cause stabilization of the protein against proteolytic degradation or induce transcriptional activation of the receptor protein.[49]

Inappropriate AR hyperactivity may also be caused by activation of coregulators. Recurrent CWR22 tumors were found to harbor overexpressed transcriptional intermediary factor 2 and steroid receptor coactivator 1, which increased AR transactivation at physiologic androgen concentrations.[37] Other coregulators of AR function include ARA70, p300, CBP, Tip60, ARA55, ARA54, gelsolin, Stat3, and RAC3.[50–53] The Foxa1 and Foxa2 proteins are transcription factors belonging to the forkhead box A (Foxa) superfamily (also known as hepatocyte nuclear factor 3 proteins) that are essential for endodermal development and are involved in respiratory, intestinal, and hepatic gene expression.[54–60] Although Foxa1 was found to be expressed in prostatic carcinomas of different grades, Foxa2 stimulates transactivation of the PSA promoter in an androgen- and AR-independent manner and has been identified in small cell carcinomas and high-grade adenocarcinomas of the prostate, suggesting that Foxa2 regulation of gene expression may contribute to progression of prostatic carcinomas to a more aggressive and androgen-independent state.[58]

Genome-wide expression analyses[61] have identified genes that are differentially expressed in prostate cancers from patients who had received the gonadotropin-releasing agonist goserelin and AR antagonist flutamide for 3 months. Hierarchical clustering algorithms that analyzed gene expression profiles classified the specimens according to treatment status, suggesting that distinct transcriptional programs are activated in prostate carcinomas in response to androgen therapy. The genes that were more highly expressed in carcinomas treated with androgen ablation agents included those encoding AR and steroid biosynthetic enzymes, as well as a suite of genes that have been previously shown to be targets of AR or have been implicated as being regulated by it, including the gene encoding PSA (kallikrein-related peptidase 3), *KLK3*, and *KLK2*, as well as *DBI, FASN, IL6, SERPINB5, TGFBR3, TMPRSS2, TUBA1, HOXC6, TRG*, and *FOLH1*.[61–66] Other upregulated genes may represent secondary, indirect effects of androgen ablation that occur later than reactivation of AR. To identify only those genes that are subject to transcriptional regulation by AR, gene expression profiles of LNCaP human prostatic adenocarcinoma cells were examined after androgen withdrawal.[61] Approximately 25% of the genes differentially expressed in carcinomas after chronic androgen ablation therapy also showed an altered transcript level in the carcinoma cell line. Finally, comparison of the gene expression profiles of androgen-resistant cancers to those of cancers that had not developed resistance demonstrated that prostatic adenocarcinomas resistant to androgen ablation therapy had gene expression profiles more similar to those of untreated, androgen-dependent tumors than of cancers under conditions of androgen deprivation. This finding suggests a reversal in the gene expression profile of androgen-refractory cancers that is caused by androgen deprivation therapy, possibly by ligand-independent reactivation of AR, a mechanism that has been proposed by several authors.[67–70] Furthermore, a unique set of genes was expressed in androgen-resistant prostatic carcinomas that was not expressed in primary androgen-dependent tumors or in other metastatic carcinomas.[61]

Activation of AR can be highlighted by immunohisto-

chemistry as a strong nuclear expression in androgen-resistant prostate cancers.[61] Moreover, reactivation of AR gene was not due to gene amplification in most cases, as it was shown by FISH analysis that only a minority of the androgen-resistant carcinomas studied contained amplified AR genes. The human prostatic adenocarcinoma xenograft CWR22, which is propagated in nude mice, recapitulates the properties of in vivo prostate cancers, with an initial period of androgen-dependent proliferation followed by persistent growth several months after androgen deprivation.[71,72] Androgen receptor protein from a relapsed CWR22 carcinoma has a half-life that is 2 to 4 times that of AR from LNCaP cells, demonstrating that recurrent tumors have hyperstabilized AR as compared to androgen-dependent neoplasms.[73] The increased expression, greater stability, and nuclear localization of AR in recurrent prostate cancers resistant to androgen deprivation correlated with hypersensitivity to low levels of androgens in these tumors; androgen ablation–resistant prostate cancers required a significantly much lower concentration of dihydrotestosterone than that required by androgen-dependent tumors for stimulation of proliferative activity.

Several of the genes that were found by the microarray study to be more highly transcribed in androgen ablation–resistant tumors encoded biosynthetic enzymes involved in the synthesis of cholesterol, including HMG-CoA synthase, squalene synthase, lanosterol synthase, and squalene monooxygenase, the rate-limiting enzyme in sterol synthesis.[61,74] Androgen ablation–resistant tumors were shown to be more strongly immunoreactive for squalene monooxygenase than were androgen-dependent tumors.[61] The increased production of steroid biosynthetic enzymes in resistant tumors suggests that one mechanism by which these carcinomas overcome androgen deprivation is by compensatory synthesis of androgens, with consequently increased AR activity. Recurrent prostatic carcinomas consistently exhibit decreased expression of the tumor suppressor gene *PTEN* (phosphatase and tensin homolog), which carries loss-of-function mutations in advanced prostate cancers.[75] The PTEN protein dephosphorylates phosphatidylinositol-3,4,5-trisphosphate (PIP_3), resulting in inhibition of the Akt (protein kinase B) cell survival signaling pathway.[76]

Besides reactivation of AR and loss of PTEN tumor suppressor activity, other mechanisms for the development of hormone-resistant prostate cancers have been proposed. Aberrant overexpression or amplification of the *HER2/neu* gene has been identified in prostatic carcinomas[77] and elevated serum levels of the HER2/*neu* extracellular domain were found in androgen ablation–refractory prostate cancers.[78] Overexpression of the HER2/*neu* (ERBB2, CD340) receptor tyrosine kinase was capable of rescuing LNCaP cells from the antiproliferative effect of androgen deprivation and also shortened the latency period for tumor formation in castrated mice with severe combined immunodeficiency by 50%.[77] Furthermore, HER2/*neu* can enhance by 15-fold the expression of the AR target *PSA* in the absence of androgens in LAPC-4 cells.[77] HER2/*neu* can also activate MAP kinase and PIP_3/Akt signaling cascades, culminating in the phosphorylation of serines 213 and 791 of AR.[79,80] Constitutive Akt activity led to increased neoplastic growth in LNCaP xenografts.[81] Other growth factors that may contribute to the development of hormone-resistant cancers include insulin-like growth factor 1, epidermal growth factor, keratinocyte growth factor, and factors secreted by neuroendocrine cells.[82–84]

The conserved basic helix-loop-helix transcription factor TWIST has been shown to be highly expressed in the majority (90%) of prostate cancers and only in a minority (6.7%) of benign prostatic hyperplasia cases.[85] TWIST expression levels were also found to be proportional to Gleason grade, and higher levels correlated with metastasis.[85] Experiments with DU145 and PC-3 androgen-resistant prostatic adenocarcinoma cell lines[85] found that down-regulation of TWIST expression by RNA interference led to suppression of invasiveness and a reduction in E-cadherin expression, as well as loss of the morphologic and molecular changes that signify the epithelial-mesenchymal transition.

In summary, a major clinical challenge presented by prostate cancer is the treatment of androgen ablation–resistant carcinomas. Recent experimental evidence suggests that there are multiple avenues leading to the development of this aggressive form of prostatic carcinoma, which subvert the molecular mechanisms of the cell to reactivate AR, activate its targets, gain inappropriate HER2/*neu* activity, lose PTEN-mediated tumor suppression, or stimulate the epithelial-mesenchymal transition via TWIST. Other authors postulate the existence of androgen-resistant prostate cancer stem cells that contribute to the growth of aggressive tumors. Future molecular studies will help further elucidate the diverse signaling pathways underlying the pathogenesis of prostate cancers refractory to systemic hormonal deprivation and may lead to the development of multiple pharmacologic agents and therapeutic modalities that will halt progression of hormone-naïve tumors.

MOLECULAR BIOLOGY OF *TMPRSS2:ERG* TRANSLOCATION

A significant role for the *ETS* gene family, which encodes transcription factors in prostate cancer, was recently discovered by using a novel bioinformatics approach known as *COPA* (cancer outlier profile analysis)[86] that identified the oncogenes *ERG* (21q22.2), *ETV1* (7p21.2), *ETV4* (17q21), and *ETV5* (3q27) as very highly expressed in a subset of prostate cancers on the basis of a large set of microarray data.[86–88] ERG, ETV1, ETV4, and ETV5 are members of the ETS family of transcription factors, which are characterized by an evolutionarily conserved, 85–amino acid DNA-binding domain that facilitates binding to purine-rich DNA with a GGAA/T core consensus sequence.[89] ETS proteins function cooperatively with other transcription factors in the regulation of a diversity of cellular functions including proliferation, differentiation, angiogenesis, hematopoiesis, oncogenic transformation, and apoptosis.[90] Importantly, translocations involving members of the *ETS* family have been identified in human leukemia and solid tumors.[89] A mechanism underlying *ETS* overexpression in prostate cancer was established once it was recognized that the androgen-responsive gene *TMPRSS2* (see below) is fused to the coding region of an *ETS* family member (for example *ERG*) as a result of gene rearrangement, which was also demonstrated directly by studies in vitro.[86,91,92] The *TMPRRSS2:ERG* gene fusion is observed in greater than 90% of prostate cancers with *ETS*-family gene rearrangements,[93] whereas *TMPRSS2:ETV1, TMPRSS2:ETV4,* and *TMPRSS2:ETV5* rearrangements occur more rarely. Furthermore, *ETV1, ETV4,* and *ETV5* have additional fusion partners other than

TMPRSS2, including *SLC45A3, HERV-K_22q11.3, C15orf21,* and *HNRPA2B1*.[94]

TMPRSS2 is located at 21q22.2,[95] and *TMPRSS2* is predominantly expressed in luminal epithelial prostate cells, with much lower expression in pancreas, kidney, lung, colon, and liver and no measurable expression in testes, ovary, placenta, spleen, thymus, circulating leukocytes, brain, heart, or skeletal muscle.[96,97] *TMPRSS2* and *ERG* are located 3Mb apart on chromosome 21q22.2-22.3 (Figure, A through E). The 5′ ends of both genes are orientated toward the telomere, and *TMPRSS2* is positioned telomerically relative to *ERG*. Interstitial deletion of the intervening intronic genomic DNA is the most common mechanism for fusion and is observed in 60% to 90% of *TMPRSS2:ERG* fusion-positive prostate cancers (see below). Regions of microhomology exist in the *TMPRSS2* and *ERG* loci, suggesting that they might underlie rearrangement events during defective homologous recombination.[98]

Seventeen different types of *TMPRSS2:ERG* fusion transcripts involving various regions of the *TMPRSS2* and *ERG* genes have been identified [86,99–102]; however, 8 of these transcripts are unlikely to result in the translation of functional ERG proteins due to the introduction of premature stop codons. Of the 9 predicted functional *TMPRSS2:ERG* fusion transcripts, 2 code for normal ERG proteins, 6 code for amino-terminal–truncated ERG proteins, and 1 codes for a bona fide TMPRSS2:ERG fusion protein.[101] These studies demonstrate that expression of multiple fusion mRNAs is common, with *TMPRSS2* exon 1 fused to *ERG* exon 4 being the most frequently expressed type of *TMPRSS2:ERG* fusion. Alternative splicing of the *TMPRSS2:ERG* gene is proposed as the most likely basis for the multiple different types of fusion mRNAs observed.[99,101]

DETECTION AND PREVALENCE OF *TMPRSS2:ERG* GENE FUSION IN PROSTATE CANCER

Most *TMPRSS2:ERG* gene fusion events in patients with clinically localized prostate cancer (ie, patients identified through PSA screening who have potentially curable disease by surgical resection) are characterized by using either fluorescence in situ hybridization (FISH) or quantitative reverse transcription–polymerase chain reaction (RT-PCR). One common FISH method uses break-apart probes that bind the 5′ (ie, green) and 3′ (ie, red) ends of the *ERG* gene (Figure). In normal prostate tissue, both of these probes hybridize to the *ERG* locus and generate adjacent green and red fluorescent signals in the nucleus. In contrast, prostate cancer cells harboring rearranged *ERG* demonstrate distinct, separate green and red fluorescent signals, as the probes are split because of change in chromosome structure. One advantage of this method is that it also reveals the mechanism underlying the rearrangement by detection of the commonly occurring 3-Mb interstitial deletion between *TMPRSS2* and *ERG*. In such cases, this deletion manifests by the loss of the 5′ (green) signal in nuclei of malignant cells.

The initial report[86] identifying the *TMPRSS2:ERG* gene rearrangement demonstrated that 47% of clinically localized prostate cancers contain the *TMPRSS2:ERG* fusion, and two-thirds of these translocations are formed secondary to interstitial deletion between the *TMPRSS2* and *ERG* genes on chromosome 21q22.2-22.3. Subsequent work[101,103–106] confirms that the *TMPRSS2:ERG* rearrangement is present in approximately 50% of primary prostate cancer samples with interstitial deletion of the 5′ region of *ERG* occurring in 60% of the *TMPRSS2:ERG*-positive primary prostate cancers. Gene rearrangements involving *ETV1* and *ETV4* are rare, accounting for approximately 2% of all observed gene alterations.

MORPHOLOGY OF *TMPRSS2:ERG* PROSTATE CANCER

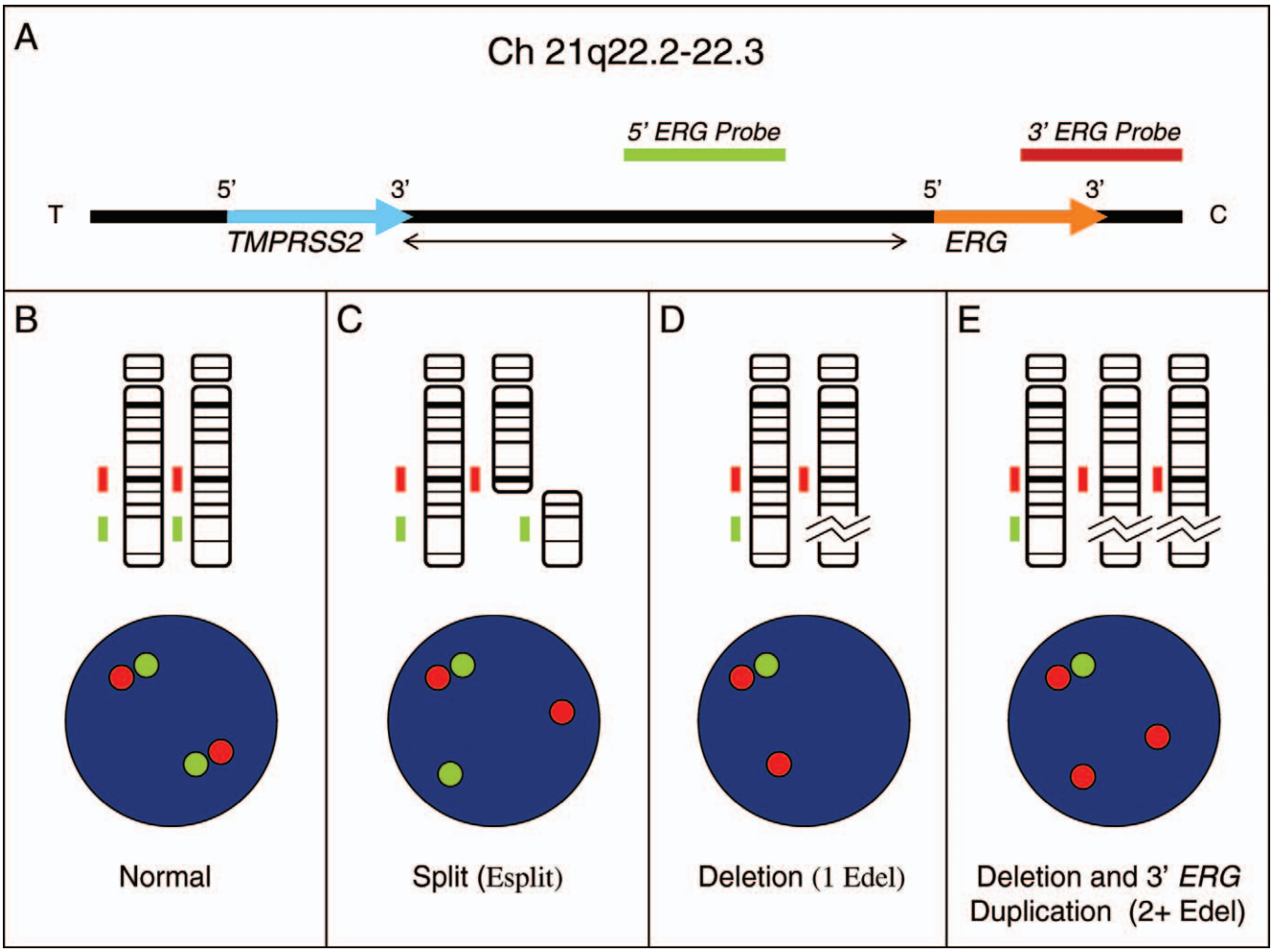
Initially, morphologic analysis of prostate cancer cases[107] identified 5 features strongly associated with the presence of the *TMPRSS2:ERG* fusion, which included blue-tinged mucin, cribriform growth pattern, macronucleoli, intraductal tumor spread, and signet ring cell features. Of the cases demonstrating none of these features, 24% were *TMPRSS2:ERG* fusion-positive. Conversely, 55%, 86%, and 93% of cases with 1, 2, or 3+ features, respectively, were *TMPRSS2:ERG* fusion-positive.

The association of the *TMPRSS2:ERG* fusion with high-grade prostatic intraepithelial neoplasia (HGPIN) was observed in up to 21% of cases in several studies.[94,108,109] Unlike localized prostate cancer, in which *TMPRSS2:ERG* fusion-positive prostate cancers typically demonstrate overexpression of *ERG*, overexpression of *ERG* is less constant in *TMPRSS2:ERG* fusion-positive HGPIN.[109] *TMPRSS2:ERG* fusions were not present in benign prostatic epithelium or other lesions not associated with prostate cancer, specifically, benign prostatic hyperplasia and proliferative inflammatory atrophy. Furthermore, all *TMPRSS2:ERG*-positive HGPIN cases identified by FISH showed the same fusion pattern as the matching prostate cancer from the same patient, and no fusion-positive HGPIN cases associated with fusion-negative prostate cancer were identified by FISH,[108,110] suggesting *TMPRSS2:ERG* may play a role in the progression from HGPIN to adenocarcinoma.[92]

Based upon (1) the homogenous distribution of the fusion gene throughout the cancer, (2) the absence of detectable *TMPRSS2:ERG* fusion events in normal and hyperplastic prostate tissue, (3) the finding that *TMPRSS2:ERG*-positive HGPIN lesions show the same fusion pattern with the matching prostate cancer, and (4) the fact that *TMPRSS2:ERG* fusion-positive HGPIN is never observed with fusion-negative matching prostate cancer, it can be suggested that *TMPRSS2:ERG* fusion is an early event in the development of prostate adenocarcinoma. In support of these findings, transgenic mice expressing the equivalent truncated *ERG* gene coded by human *TMPRSS2:ERG* develop mouse PIN (mPIN), along with loss of the p63-positive basal layer adjacent to mPIN foci.[92] These findings strongly suggest that *TMPRSS2:ERG* fusion HGPIN is a true precursor for *TMPRSS2:ERG*-positive prostate cancer.

TMPRSS2:ERG AND CLINICAL PROGNOSIS

As a wide array of distinct *TMPRSS2:ERG* fusions have been identified, several studies have explored whether specific gene fusion isoforms correlate with aggressive clinical behavior. One group[101] observed that expression of *TMPRSS2:ERG* fusion variants consisting of exons 1 and 2 of *TMPRSS2* fused to exon 4 of *ERG* (T2E4) and, to a lesser extent, exon 1 of *TMPRSS2* juxtaposed to exons 2 or 3 of *ERG* (T1E2/3) are associated with early recurrence and seminal vesicle invasion. Interestingly, these fusion isoforms all contain the native ATG translation initiation codon from either *TMPRSS2* or *ERG*, raising the possibility that increased efficiency of translation from native translation start codons may underlie the correlation be-



Model of TMPRSS2:ERG *gene rearrangements and fluorescence in situ hybridization (FISH) patterns observed in prostate cancer. A, Physical map of the* TMPRSS2 *and* ERG *loci on 21q22.2-22.3. T and C orientate toward the telomeric and centromeric regions, respectively. 5′ ERG (green) and 3′ ERG (red) FISH break-apart probes are positioned above the chromosome relative to where they hybridize. The* TMPRSS2 *and* ERG *loci are separated by approximately 3 Mb. B, Chromosome structure (upper) and nuclear FISH pattern (lower) observed in a normal* ERG *locus. This pattern is observed in approximately 50% of all clinically localized prostate cancers. C, Separated 5′ ERG and 3′ ERG loci due to gene rearrangement. This pattern has been referred to as Esplit (see text). Note the retention of both the 5′ ERG and 3′ ERG FISH probe signals. D, Chromosome structure and nuclear FISH pattern observed with an interstitial deletion of the 5′ ERG locus. Note the loss of the 5′ FISH probe signal. This is the most common* TMPRSS2:ERG *gene rearrangement pattern observed in prostate cancer and has been referred to as 1Edel. E, Interstitial deletion of the 5′ ERG locus accompanied by a duplication of 3′ ERG sequence. Note the loss of the 5′ FISH probe and duplication of the 3′ FISH probe signals. This pattern of* TMPRSS2:ERG *gene rearrangement is associated with a worse clinical prognosis and has been referred to as 2+Edel.*

tween *TMPRSS2:ERG* fusion type and aggressive clinical course. Alternatively, it may represent altered biochemical properties of the TMPRSS2:ERG fusion protein.

A comprehensive FISH analysis of *TMPRSS2:ERG* rearrangement in 445 cases[111] has demonstrated that prostate cancer in which the 5′ portion of *ERG* is deleted has significantly worse cause-specific and overall survival than prostate cancer in which *ERG* is either not disrupted (ie, normal *EGR*) or contains a balanced *ERG* translocation (ie, split *EGR*). When *ERG*-deleted prostate cancers were further analyzed, the authors observed that prostate cancer with 2 or more copies of the 3′ ERG region showed much worse clinical behavior: the survival rate of patients with duplication of the *TMPRSS2:ERG* gene rearrangement was 25% at 8 years compared to 90% for patients with prostate cancer without *ERG* rearrangement. A separate study examining 521 patients[112] reported similar results in which duplication of *TMPRSS2:ERG* was associated with higher clinical stage and aggressive disease. Furthermore, analysis of 214 patients with prostate cancer suggested that multiple copies of *TMPRSS2:ERG* were associated with greater prostate cancer–specific mortality, although this study[113] was not statistically significant. Taken together, these results demonstrate that *ERG* gene copy number may provide useful prognostic information for patients with prostate cancer.

The association of *TMPRSS2:ERG* gene rearrangement with Gleason score, aggressive disease, and prognosis is unclear, as multiple studies with conflicting findings have been described. A population-based study[114] of 252 men followed up expectantly with low-stage (T1a-bNXM0) prostate cancer explored the risk of metastasis or prostate cancer–specific death based upon the presence of the *TMPRSS2:ERG* fusion. These authors determined that *TMPRSS2:ERG* fusion-positive prostate cancer is associated with higher Gleason score (>7) than fusion-negative

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