Background. The TMPRSS2-ERG gene fusion is one of the most widely spread chromosomal rearrangements in carcinomas. Since its discovery, a number of studies have examined its diagnostic, prognostic and therapeutic implications for prostate cancer where suitable biomarkers are still lacking. The publication data are inconsistent. The aim of this review was to critically evaluate the current clinical impact of this gene fusion.

Methods. The PubMed online database was used to search relevant reviews and original articles.

Results. Although the TMPRSS2-ERG gene fusion appears to be a suitable diagnostic biomarker, the prognostic implications of this gene fusion are still unclear. Several new strategies for therapeutically targeting ETS fusions and their modulators have been identified and are currently being investigated.

Conclusion. Due to the heterogeneity of prostate cancer, the combination of several biomarkers is necessary to accurately assess the presence of prostate cancer, predict its potential clinical outcome and decide on appropriate therapy (e.g., PARP inhibitors).

Key words: TMPRSS2-ERG, gene fusion, diagnosis, prognosis, predictive marker, prostate cancer

INTRODUCTION

Prostate cancer (PCa) is the third most common cancer diagnosed in Europe today, and the most frequent cancer in European men. It is a heterogenous disease displaying either an indolent or an aggressive course. One of the major problems with its diagnosis and prognosis, is the lack of valid biomarkers. Elevated levels of serum prostate-specific antigen (PSA) and/or abnormal digital rectal examination (DRE) which form the rationale for histopathological examination by needle biopsy, are insufficient and can lead to overdiagnosis and overtreatment. It is also impossible to distinguish between indolent and aggressive forms of PCa (ref.3). The main focus of current PCa research is hence on identifying and validating new biomarkers. This review covers recent knowledge on the importance of the TMPRSS2-ERG gene fusion in PCa.

GENES FUSIONS AND THEIR SIGNIFICANCE

Gene fusions resulting from chromosomal rearrangements are known to play an important role in the initial steps of tumorigenesis. Tomlins et al. first described a gene fusion between TMPRSS2 (Transmembrane Protease Serine 2) gene and ETS (Erythroblastosis Virus E26 Transformation-Specific) family genes in PCa, involving the 5'-untranslated region of TMPRSS2 (21q22) and the encoding region of some transcription factors such as the ETS-related gene (ERG, 21q22) or ETS variant 1 gene (ETV1 7p21). Bioinformatic analysis of DNA microarray data, subsequent fluorescence in situ hybridization (FISH) and reverse transcription polymerase chain reaction (RT-PCR) analysis, have identified TPRSS2-ERG fusion and TMPRSS2-ETV1 fusion in 16/29 (55%) and in 7/29 (27%) cases of PCa, respectively. Until this time, carcinomas were believed to harbor only rare disease-specific gene rearrangements, unlike leukemias, lymphomas and sarcomas.

TMPRSS2 is a prostate-specific, androgen regulated gene, constitutively expressed under the transcriptional control of androgens through androgen responsive elements (ARE) in its 5’UTR. The ETS family of transcription factors is one of the largest families of transcription regulators. All 27 members share a conserved DNA binding domain – the ETS-domain which permits binding to purine rich DNA sequences containing a 5’-GGAA/T-3’ core sequence. ETS transcription factors play an important role in diverse biological processes, including cell proliferation, apoptosis, differentiation, angiogenesis and invasiveness. TMPRSS2-ETS gene fusions lead to increased expression of the ETS members in response to the androgen induced TMPRSS2 promoter.

Further experiments revealed that the TMPRSS2 gene could also be fused to other members of the ETS transcription factor family, such as ETV4 and ETV5 genes. Likewise, other genes, for example, SLC45A3 (Solute Carrier Family 45, Member 3), NDRG1 (N-Myc Downstream Regulated 1), HERPUD1 (Homocysteine-Inducible, Endoplasmatic Reticulum Stress-Inducible, etc.) genes.
Ubiquitin-Like Domain Member 1) may fuse with the 3’ region of ETS family members. However, the TMPRSS2-ERG gene fusion accounts for most recurrent gene fusions in PCa (ref.19), with a frequency of 40-70%, which provides an idea of its potential as a biomarker4,20.

On the base of the above, PCa can be divided into two distinct molecular subtypes, ETS fusion-positive and ETS fusion-negative, characterized by a different biological behavior and response to therapy4,21-23.

INCIDENCE OF PROSTATE CANCER AND TMPRSS2-ERG

The incidence of PCa shows geographical and ethnic differences. The Asian population has a lower incidence of PCa than Caucasians, a difference purported to entail gene and lifestyle differences. The ETS gene fusion rate is highest in the United States (42-60%) and lowest in Asia (21% in Korea and 28% in Japan) (ref.24,25). Mosquera et al.26 examined 100 prostate biopsy specimens from United States patients and reported that non-Caucasian patients were less likely to have a positive TMPRSS2-ERG fusion status than Caucasian patients. These genetic differences may underlie the regional/ethnic differences in clinical incidence and might be induced by specific environmental and/or genetic risk factors27.

The TMPRSS2-ERG gene fusion is an early event in carcinogenesis and absent in benign prostatic hyperplasia (BPH) and proliferative inflammatory atrophy (PIA). The gene fusion is found in approximately 20% of high-grade prostatic intraepithelial neoplasia (HGPIN) lesions, and in around 50% of localized cancers6,28-32.

MECHANISM OF FUSION FORMATION

The relatively high frequency of the TMPRSS2-ERG gene fusion in PCa is the result of co-localization of both genes (TMPRSS2, ERG) on chromosome 21q22.2. The fusion of both genes is most often generated by an interstitial deletion where a region of approximately 2.8 Mb in the 21q22 locus is lost (known as Edel class), and to a lesser extent through an insertion of intervening region into another chromosome (known as Esplit class) (ref.4,33-35). The mechanism of fusion formation is summarized in Fig 1. The deletion of intervening region is observed in 39-60% of TMPRSS2-ERG-positive cases36,37. Roughly, 13 genes located in the area of the common deletion site are down-regulated. In addition to the oncogenic potential of the TMPRSS2-ERG fusion product, loss of at least two of these genes, ETS2 (V-Ets Avian Erythroblastosis Virus E26 Oncogene Homolog 2) and HMGN1 (High Mobility Group Nucleosome Binding Domain 1) may be associated with cancer progression36,38.

Mani et al.39 demonstrated that androgen signalling induces chromosomal proximity between TMPRSS2 and ERG loci, and facilitates the formation of the TMPRSS2-ERG gene fusion when subjected to enzyme TOP2B [Topoisomerase (DNA) II Beta 180kDa], that causes DNA double-strand breaks (DSBs). This enzyme catalyzes transient DSBs to resolve DNA topological constraints.

Fig 1. Mechanism of fusion formation. A. The fusion of TMPRSS2 and ERG gene generated by an interstitial deletion, where a region of 2.8 Mb is lost (red line). B. The fusion of TMPRSS2 and ERG gene generated through an insertion of interstitial region into another chromosome in genome.
Androgen-induced TOP2B mediated DSBs are highly recombinogenic and could lead to de novo production of TMPRSS2-ERG fusion transcripts. TOP2B-mediated DSBs occurring during regulated transcription represents a new paradigm for development of DSBs involved in generating gene rearrangements in cancer.40,41. On the base of genome-wide linkage analysis, Luedeke et al.42 found significant association of TMPRSS2-ERG fusion-positive PCa and rare variants in the genes POLI [Polymerase (DNA Direct) iota (variant F532S)] and ESCO1 [Establishment Of Sister Chromatid Cohesion N-Acetyltransferase 1 (variant N191S)]. Both genes encode proteins involved in the repair of DNA DSBs, thereby protecting the chromosomal stability and preventing translocation events such as TMPRSS2-ERG fusion.

**FUSION TRANSCRIPT ISOFORMS**

TMPRSS2-ERG gene fusions are one of the most common genetic events in PCa and account for 80-90% of PCa fusions.4,36,38,43. Several studies have revealed more than 20 TMPRSS2-ERG transcript variants, which arise both as a result of alternative splicing or of recombination mechanisms (e.g. interstitial deletions, insertions, translocations) (ref.10). The most common TMPRSS2-ERG isoform consists of exon 1 of TMPRSS2 fused to exon 4 of ERG. Heterogeneity has been identified in the location of the TMPRSS2-ERG fusion junction and in the exons of ERG present in the fusion transcript. Wang et al.44 showed that both the presence of certain isoforms of TMPRSS2-ERG fusion and their expression level, may affect PCa progression. For example, the isoform consisting of exons 1-2 of TMPRSS2 fused to exon 4 of ERG is associated with features of aggressive PCa. Although overexpression of full-length ERG protein promotes the transcriptional activation of oncogenes and facilitates cancer progression, some N-terminal truncated ERG proteins encoded by TMPRSS2-ERG fusion genes, might inhibit oncogenic transcriptional activation by competitively binding to ETS domain binding sites in gene fusion positive prostate cancer. PCas expressing these types of truncated ERG proteins might possess less aggressive features.45.

**HETEROGENEITY OF TMPRSS2-ERG IN PROSTATE CANCER**

The majority of primary PCas arise multifocally.46. PCa is a heterogeneous group of diseases originating in multiple independent clonal expansions, as confirmed by discordant patterns of allelic loss among various tumor foci.47,48. Approximately 75% of whole-mount radical prostatectomy specimens have multiple cancer foci. Recently, several groups have examined ETS fusions in the context of multifocal cancer. All groups showed that from 41% to 67% of cases harbor individual cancer foci that differ with regard to the presence or absence of ETS fusions or a fusion mechanism (i.e. rearrangement through deletion or insertion) (ref.4,31,49-52). This observed interfocal heterogeneity supports the hypothesis that prostate carcinogenesis may be a multicentric process, in which at least two independent pathogenetic pathways coexist in the same prostate, leading to independent neoplasias with or without the involvement of the ETS pathway.50. Intrafocal heterogeneity has also been described.52,53,54. Svensson et al.53 found cases showing intrafocal heterogeneity (i.e., both rearranged and non-rearranged nuclei in the same cancer focus), and cases where the same gene rearrangement showed both types of rearrangement mechanisms (i.e., rearrangement through insertion and deletion) within the same focus. The molecular heterogeneity may be the result of tumor progression and may lead to different tumor types and clinical outcomes.55.

Several studies have demonstrated the presence of TMPRSS2-ERG gene fusion in most cases of metastatic PCas (ref.37,36,57). In unifocal PCa, the status of the ERG rearrangement was concordant for the primary PCa and metastasis. In multifocal PCa, despite a significant inter focal discordance, the status of the ERG rearrangement was concordant for the dominant primary tumor focus and metastasis. The concordance of the ERG gene rearrangement status for the dominant primary tumor focus and metastasis suggests that metastasis most likely arises from the dominant tumor focus in multifocal PCas (ref.50). However, in 17% of cases, TMPRSS2-ERG can be linked to the dominant tumor. However, in 17% of cases, TMPRSS2-ERG is seen in secondary tumors. This result also suggests that in a small proportion of cases, the secondary tumors can also have considerable alterations that may be biologically significant. Moreover, Perner et al.56 also reported that multifocal PCa can demonstrate both ERG-positive and ERG-negative foci and that the positive foci have a greater predilection for metastasis. This has potential clinical impact on disease progression and therapeutic intervention. On the other hand, Guo et al.58 found that the metastasis may also arise from the tumor focus without rearrangement of the ERG gene in multifocal PCa. Mehra et al.37 discovered that TMPRSS2-ERG gene fusion in all metastases was associated with deletion of the 5’ ERG gene. However, Attard57 and Guo58 found that TMPRSS2-ERG gene fusion in metastases was associated with translocation of the 5’ ERG gene. Therefore, TMPRSS2-ERG gene fusion in metastatic PCa is not exclusively associated with deletion of the 5’ ERG gene. Different tumor foci of multifocal primary PCa may differ in the presence of TMPRSS2-ERG gene fusion and in fusion mechanism, while all metastatic sites display identical ETS rearrangement status (fusion positive or negative), and the same fusion mechanism, when TMPRSS2-ERG gene fusion is present.
INTERPLAY OF TMPRSS2-ERG WITH SIGNALLING PATHWAYS

Zong et al. found that increased expression of ETS proteins in adult murine prostate epithelial cells is sufficient to induce epithelial hyperplasia and focal prostatic intraepithelial neoplasia (PIN) lesions, but not progression to carcinoma. ERG interacts with alterations in PI3K (Phosphatidylinositol 3-Kinases) signalling, such as PTEN (Phosphatase And Tensin Homolog) inhibition or AKT1 (V-Akt Murine Thymoma Viral Oncogene Homolog 1) up-regulation, to cause the development of a well-differentiated adenocarcinoma. Loss of PTEN and the presence of the TMPRSS2-ERG gene fusion are events significantly associated with PCa (ref.60). Bismar et al. hypothesize that PCa development may be driven initially by PTEN genomic hemizygous loss, causing HGPIN lesions. Monoallelic PTEN inactivation leads to genomic instability which may facilitate the chromosomal rearrangement leading to gene fusion formation and progression to cancer. Subsequent biallelic PTEN inactivation, by either homozygous deletion or deletion of one allele and mutation of the other, characterizes a particularly aggressive subset of metastatic and hormone-refractory PCas (ref.61).

ERG overexpression in PCa is highly implicated in promoting motility and invasiveness, and is associated with elevated levels of HDAC1 (Histone Deacetylase 1) and subsequent down-regulation of HDAC1 targeted genes, activation of WNT/β-catenin signalling pathway and inhibition of apoptotic signalling. HDAC1 upregulation is common in PCa, but was found to be uniformly increased in tumors with ERG rearrangement. Activation of the androgen receptor (AR) through the WNT/β-catenin signalling results in increase in AR transcription and expression, enhanced transcription of TMPRSS2-ERG and high levels of ERG (ref.62). Overexpression of AR alone does not stimulate hyperplastic lesions, but when combined with high levels of ERG, it promotes the development of more poorly differentiated, invasive adenocarcinomas63. Elevated ERG, as a result of the TMPRSS2-ERG gene fusion, modulates the growth of PCa cells by upregulating the MYC oncogene and by abrogating the differentiation of prostate epithelium64. Elevated MYC expression in primary prostate tumor is biologically relevant and may be a predictor of future biochemical recurrence65. ERG can shut-down androgen signalling by blocking the AR expression, thereby preventing the normal development of prostate cells. Furthermore, ERG induces repressive epigenetic programs via direct activation of the H3K27 methyltransferase EZH2 (Enhancer Of Zeste Homolog 2), a member of the Polycomb-group (PcG) family. In this model, TMPRSS2-ERG plays a crucial role in cancer progression by disrupting lineage specific differentiation of the prostate and potentiating the EZH2-mediated dedifferentiation program66.

Riberio et al. reported an association of ERG expression with expression of several genes encoding metabolic enzymes or extracellular/transmembrane proteins involved in cell adhesion, matrix remodeling or signal transduction pathways. They also observed significant overexpression of CRISP3 (Cysteine-Rich Secretory Protein-3) in fusion-positive PCas compared with non-malignant tissue or fusion-negative PCas. They further confirmed a strong correlation between ERG and CRISP3 mRNA levels. The presence of ERG genomic rearrangement and ERG and CRISP3 mRNA overexpression were both associated with pT3 locally advanced tumors. Ultimately they proved that CRISP3 protein is a direct target of overexpressed ERG, suggesting that CRISP3 may be a mediator of tumor progression driven by the TMPRSS2-ERG rearrangement.

TMPRSS2-ERG GENE FUSION AS A PROGNOSTIC MARKER

The prognostic implications of TMPRSS2-ERG gene fusion in PCa are still unclear. Since 2005, when Tomlins' first described the presence of this fusion in PCAs, a large number of studies have been published in this field. Some authors found a correlation between the presence of fusion and poor prognoses16,46,69-71, but others found a correlation between the presence of fusion and good prognosis72,74 or no correlation71,75-78. The prognostic value of TMPRSS2-ERG rearrangements in selected studies is summarized in Table 1. It seems that earlier studies tended to interpret TMPRSS2-ERG gene fusion as a marker of poor prognosis and recent large cohort studies as a marker of better prognosis but most of the data suggest a trend towards unfavourable disease outcome in the presence of gene fusion69. There are several explanations for these controversial observations such as clinical settings (surgical or other interventions immediately after diagnosis versus conservative management), size of patient cohorts, differences in sample collection and in the technique used for determination of gene fusions60-79. Crucial issues are the definitions of study endpoints such as biochemical failure (rise in serum PSA after prostatectomy) versus overall/disease-specific survival80. The discordant results may also be caused by the actual characteristics of PCAs, such as PCa heterogeneity, the presence of the fusion variants and geographical and/or ethnic differences70.

Attard et al. found that patients with two or more copies of the TMPRSS2-ERG fusion gene (due to the interstitial deletion - Edel) had worse survival rates than patients without TMPRSS2-ERG rearrangement. This is consistent with the view that ERG overexpression is responsible for driving cancer progression, and that the 2.8 Mb deletion (containing genes with tumour suppressor activity) may contribute to the oncogenic potential of the TMPRSS2-ERG fusion product67.

In contrast to Attard et al., Gopal et al. reported that TMPRSS2-ERG rearrangement alone was not associated with clinical outcome but with lower grade cancers. These authors described a subgroup of cancers with increased copy number of TMPRSS2-ERG loci, which were more clinically aggressive. These PCAs were predominantly aneuploid/tetraploid and shared additional chromosomal abnormalities. They therefore concluded that the aggressive clinical behaviour is associated with
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IHC, immunohistochemistry; CNI, copy number increase
increased copy number of chromosome 21 and reflect generalized aneuploidy rather than copy number increase of rearranged TMPRSS2-ERG. Findings consistent with this were published by Toubaji et al.\textsuperscript{29}. They reported that TMPRSS2-ERG gene fusion was not associated with PCa recurrence, supporting the lack of prognostic significance of the ERG gene fusion determined by FISH. In contrast, they found that ERG gene copy number gain without fusion was associated with twice the risk of PCa recurrence. The ERG gene copy number increase is explained as the result of tumor aneuploidy, potentially leading to chromosome 21 polysomy. In this context, the association of greater probability of tumor progression with increased copy number of the ERG gene formed without fusion is not surprising given the previous evidence supporting aneuploidy as a negative prognosticato in Pca (ref\textsuperscript{30,33}).

**CLINICAL IMPLICATIONS**

Serum PSA monitoring is widespread and clinically used for following up PCa development but it has several limitations as an early detection marker\textsuperscript{22,\textsuperscript{24}}. The estimated frequency of PSA screening-detected cancers which never manifest as clinical symptoms is 23 to 44\% (ref.\textsuperscript{15}) but early detection of PCAs can increase the curative success rate\textsuperscript{8}. Therefore, it is necessary to search for new early biomarkers. Due to PCa heterogeneity, the use of marker panels can further improve the diagnostic and prognostic sensitivity\textsuperscript{37,38}. Recently, attention has focused on PCA3 (Prostate Cancer Antigen 3) a prostate specific non-coding RNA, highly overexpressed in PCa and which may be detected in urine\textsuperscript{8}. Many studies have shown that a PCA3-based urine test can improve the specificity of PCa diagnosis\textsuperscript{50,53}. Similar to PCA 3, the TMPRSS2-ERG fusion transcript can be detected in urine and this improves PCa diagnostics. TMPRSS2-ERG gene fusion analysis in combination with urine PCA 3 analysis enhances the probability of PCa detection. The introduction of new urinary biomarkers PCA3 and TMPRSS2-ERG into clinical practice could lead to a considerable reduction of prostate biopsies\textsuperscript{84}.

Prostate small cell carcinoma is a relatively rare type of PCa with aggressive clinical outcome. It is difficult to distinguish prostate small cell carcinoma from bladder small cell carcinoma especially in small biopsy samples. Four independent studies showed that the frequency of ERG alterations in prostate small cell carcinoma is the same as in adenocarcinoma\textsuperscript{68,69}. Thus, ERG rearrangement was found in approximately half of tested prostate small cell carcinoma samples, but was not detected in small cell carcinoma of another origin (for example bladder small cell carcinoma or lung small cell carcinoma). Although the sensitivity of this marker is approximately 50\%, its predictive value is higher than other markers such as PSA or prostein, which are found only in 28\% of cases of prostate small cell carcinoma\textsuperscript{99}. Detection of ERG rearrangement in small cell carcinoma, and in other epithelial and non-epithelial tumors, clearly confirms the prostatic origin of tumor\textsuperscript{50,100}.

The TMPRSS2-ERG gene fusion in PCa makes it a desirable therapeutic target. It was shown that knock-down of this gene fusion product inhibited primary tumor growth\textsuperscript{101}. One recent study reported targeting the TMPRSS2-ERG gene fusion junction in vivo by specific siRNAs delivered via liposomal nanovectors. This approach resulted in tumor growth inhibition without any apparent toxicity or evidence of the native ERG protein down-regulation\textsuperscript{102}. Other approaches include using other inhibiting modulators of ETS transcription such as upstream signalling kinases or downstream targets of ERG protein to block its activity\textsuperscript{103}. Importantly, Brenner et al.\textsuperscript{104} investigated the mechanisms by which ETS gene fusions mediate their effects, and found that TMPRSS2-ERG product interacts with the enzyme PARP1 [Poly (ADP-Ribose) Polymerase 1]. This ETS:PARP1 interaction axis represent a target for therapeutic intervention, and motivates the assessment of ETS gene fusion as a potential predictive biomarker of response in future clinical trials incorporating PARP inhibitors into the treatment of PCa and other ETS fusion-positive malignancies.

**CONCLUSION**

TMPRSS2-ERG gene fusion appears to be a suitable promising biomarker for its specificity to PCa tissue, high incidence and a connection with the androgenic signaling pathways. The introduction of early and reliable diagnostic markers discriminating PCa could obviate unnecessary biopsies. The combination of prostate specific markers, such as TMPRSS2-ERG and PCA3 may be one way of improving diagnostics. The prognostic significance of the TMPRSS2-ERG gene fusion is still unclear to date. However, the occurrence of this gene fusion in small cell carcinoma can be used to determine the prostate origin of the PCa. Finally, several new strategies for therapeutically targeting ETS fusions and their modulators have been identified and are currently being investigated.

**ACKNOWLEDGEMENTS**

This work was supported in part by grants NT13573 from the Czech Ministry of Health and NPU I LO1304 from the Czech Ministry of Education.

Authorship contributions: AB, JB: literature search and manuscript design; All authors: manuscript drafting and final approval.

Conflict of interest statement: The authors state that there are no conflicts of interest regarding the publication of this article.


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