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REVIEW – CLINICAL ONCOLOGY

ERG expression in prostate cancer: biological relevance and clinical implication

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Abstract
Introduction Screening for increased levels of prostate-specific antigen (PSA) has allowed early detection of a large majority of prostate cancer (PCa) cases. However, the relative lack of specificity of PSA has resulted in significant over-diagnosis and unnecessary treatment for indolent tumors. The fusion of the transmembrane protease serine 2 with E26 transformation-specific family genes, particularly ERG, is the most widespread genetic alteration in prostate cancer, and data suggest that it is more specific for neoplastic prostate disease and may be of added prognostic value and point toward molecular subtype of PCa.
Methods In this review, retrospective studies and clinical trials were analyzed to highlight the recent advances in our understanding of the cellular consequence of ERG rearrangement, describe its interactions with other genetic and molecular pathways, and discuss its potential diagnostic and prognostic value.
Conclusion ERG over-expression has an emerging role in the diagnosis of PCa pathology, although there is still debate about its prognostic value. Elucidation of the mechanisms of ERG gene rearrangements and expression promises novel therapeutic and diagnostic avenues for prostate cancer.

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Introduction

Prostate cancer is the most common cancer diagnosed in North American men, excluding skin cancers (Siegel et al. 2015). It is estimated that in 2015, approximately 220,800 new cases and 27,540 prostate cancer-related deaths will occur in the USA (Siegel et al. 2015). While the increased use of the relatively nonspecific (PSA) testing and subsequent biopsy has led to an increase in incidence rates, mortality figures have seen much less variation (Ross et al. 2008). The overall high death toll of PCa is mostly due to recurrence of previously treated cases and progression to a largely incurable hormone refractory metastatic disease (Denmeade and Isaacs 2002; Feldman and Feldman 2001). It is becoming obvious that more specific diagnostic and therapeutic modalities are a critical unmet need in prostate cancer research.

ERG was discovered in 2005, to be the most frequently over-expressed proto-oncogene in prostate cancers, by quantitative RT-PCR, with 72 % of cases overexpressing *ERG* (Petrovics et al. 2005). In the same year, Tomlins et al. (2005) reported a recurrent genomic rearrangement in prostate cancer, resulting in the fusion of the 5′ untranslated region of the androgen-responsive transmembrane serine proteinase *TMPRSS2* with E26 transformation-specific (*ETS*) family genes. While fusion to a number of *ETS* genes, including *ETV1*, *ETV4* and *ETV5,* has been reported, the most common gene fusion identified is between TMPRSS2 (21q22.3) and ETS-related gene (*ERG*) (21q22.2), present in about half of all prostate cancers studied (Kumar-Sinha et al. 2008).

ERG background and discovery

The *ETS*-related gene (*ERG*) was first described by Reddy et al. (1987), assigned to the *ETS* oncogene family (Reddy et al. 1987; Rao et al. 1987), and is located on human chromosome 21, band q22 (Rao et al. 1988). The unique feature of the *ETS* family, including *ERG*, is the presence of the highly conserved *ETS* DNA-binding domain that binds to sequences containing a central *GGA* motif (Hollenhorst et al. 2011). Genes in the *ETS* family regulate embryonic development, cell cycle control, cell proliferation, differentiation and migration, apoptosis, and angiogenesis (Sharrocks 2001). It has been reported that *ERG* is required for hematopoiesis, adult hematopoietic stem cell function, as well as the maintenance of normal peripheral blood platelet numbers (Loughran et al. 2008).

ERG gene rearrangements in human have been found in various malignancies. Chromosomal translocation t (16; 21) (p11; q22), resulting in fusion of *TLS/FUS* to *ERG,* was identified in acute myeloid leukemia (Shimizu et al. 1993; Kanazawa et al. 2005) and acute lymphoblastic leukemia (Oh et al. 2010). *ERG* deletion was also described in a subset of acute lymphoblastic leukemia (Mullighan et al. 2007). Five to ten percent of patients with Ewing's sarcoma showed t (21; 22) translocation resulting in expression of a hybrid EWS/ERG protein (Sorensen et al. 1994). Moreover, *ERG* rearrangements have now been well documented in prostate cancer. The landmark study by Tomlins et al. (2005) discovered gene fusion of the 5′ untranslated region of *TMPRSS2* (which encodes transmembrane protease, serine 2) to the *ETS* family members *ERG* or *ETV1* in the majority of the prostate cancer cases studied. These findings have now been independently corroborated by a number of researchers, with increased ERG protein expression thought to be reflective of *ERG* gene rearrangement in prostate cancer (Chaux et al. 2011; Miettinen et al. 2011; van Leenders et al. 2011; Furusato et al. 2010; Lotan et al. 2011; Park et al. 2010). Of note, the prevalence of Prostate cancer shows a great difference between western and Asian patients (Siegel et al. 2013). It was reported that the incidence of PCa in western countries is 20 times higher than in Asian countries (Ferlay et al. 2013). Furthermore, recent studies have shown lower frequency of *TMPRSS2-ERG* fusion in Asian countries (21 and 28 % in Korea and Japan, respectively) compared to USA (42–60 %) (Wang et al. 2012). This geographical/ethnic variation might pertain to different molecular mechanisms of prostate tumorogenesis in these populations.

TMPRSS2 is constitutively expressed, downstream of androgen, in prostate tissues (Burdova et al. 2014). In cultured prostate cancer cells, androgen-dependent *ERG* gene overexpression was noted in the VCaP cell line which is androgen sensitive and harbors the *TMPRSS2-ERG* gene fusion, but not in LNCaP cells which are also androgen sensitive but do not harbor the *TMPRSS2-ERG* gene fusion (Tomlins et al. 2005). Similarly, in human prostate cancer xenografts, ERG expression was restricted to samples carrying the *TMPRSS2-ERG* fusion, but not in the androgen-insensitive samples and fusion-negative samples (Hermans et al. 2006). The focus of recent studies have been related to understanding the functional consequence of these reported gene fusions, in addition to uncovering any potential diagnostic or prognostic value.

Biological and molecular features of *ERG* gene rearrangements

The *TMPRSS2* and *ERG* genes are located about 3Mbp apart on chromosome 21, and the most common gene rearrangement seen involves the deletion of all or part of the intervening sequence (Iljin et al. 2006; Mertz et al. 2007; Perner et al. 2006). Mani et al. (2009) showed an androgen-mediated fusion mechanism in which androgen not only facilitated the chromosomal proximity between *TMPRSS2* and *ERG* gene partners, but also mediated recombinogenic double-strand breaks (DSBs) to form the gene fusion. The *ERG* gene belongs to the *ETS* family (29 members in five subfamilies) and has at least nine reported splice variants (Rao et al. 1987; Owczarek et al. 2004; Duterque-Coquillaud et al. 1993). *ERG* upregulation is seen in about half of all prostate cancers, and the upregulation is thought to occur as a result of fusion transcripts consisting of the 5′ sequences of the androgen-regulated *TMPRSS2* and the 3′ sequence of *ERG* (Mani et al. 2009).

At least twenty different break points have been identified, However, of the most common variants that exist for *TMPRSS* fusion with *ERG*, two encode full-length ERG protein, eight encode N-truncated ERG sequences, and one encodes a *TMPRSS2-ERG* fusion transcript (Hermans et al. 2008). The most common fusion transcripts involve the fusion of *TMPRSS2* exon 1 to *ERG* exon 4 and *TMPRSS2* exon 1 fused to *ERG* exon 5 (Clark et al. 2007; Svensson et al. 2014). Of note, certain *TMPRSS2-ERG* fusion isoforms have been implicated as mediators of PCa progression (Wang et al. 2006). For instance, fusion between first two exons of *TMPRSS2* and exon 4 of *ERG* tends to be associated with lethal PCa (Wang et al. 2006). There is increasing evidence showing that TMPRSS2 is involved in metastasis and invasion pathways in the prostate via triggering protease-activated receptor-2 (Wilson et al. 2005). In vivo mice studies showed that either overexpressing of ERG or inducing *TMPRSS2-ERG* fusions did not develop invasive prostate cancer (Klezovitch et al. 2008). Interestingly, microinvasive cancers were found enriched in *ERG* mice with PTEN-loss heterozygous background (Carver et al. 2009). These findings raise the possibility that ERG cross talk with other oncogenes or tumor suppressors to develop prostate cancer pathology.

Several studies have correlated whole-genome gene expression profiling with clinical data, obtained from ERG-overexpressing PCa samples, to pinpoint relevant signal transduction pathways. For example, Iljin et al. (2006) demonstrated that the WNT pathway was associated with ERG overexpression in PCa cancer. Another study reported the role of the transforming growth factor β (TGF-β) pathway in ERG-overexpressing PCa pathology (Brase et al. 2011). Although the exact regulating mechanism of *ERG*-associated genes remains unclear, quite a few studies have reported multiple genes regulated by *ERG*, either directly or indirectly (Iljin et al. 2006; Brase et al. 2011; Bismar et al. 2014). However, despite the magnitude of information published on this subject in the recent few years, an important question about whether *ERG* and *ETV1* function the same way in PCa pathology remains unanswered. Although *ERG* and *ETV1* belong to the same *ETS* superfamily and both have common binding sites, they exert opposite effects on *AR*-mediated gene pathway (Baena et al. 2013). Using expression data from localized PCa samples, *ERG* and *ETV1* downstream genes show differential clustering patterns (Boormans et al. 2010). The exact biological and molecular mechanisms of *ETV1* overexpression in PCa remain to be investigated.

ERG-related gene signatures and potential targets

TMPRSS2-ERG fusion has been reported present in about 50 % of surgically treated PCa cohorts (radical prostatectomy series); it is less common in high-grade prostatic intraepithelial neoplasia (HGPIN) averaging about 11 % (Mosquera et al. 2008; Park et al. 2014). Additionally, in mice models, overexpression of *TMPRSS2-ERG* alone is not sufficient to induce prostate neoplasia, which is accelerated in the presence of *PTEN* genomic deletions (Carver et al. 2009; King et al. 2009). This has led to the question of whether *TMPRSS2-ERG* is an early event in PCa pathogenesis and whether it can predict pathways related to HGPIN progression to invasive cancer. Previous studies have focused on identifying genetic signatures related to *ERG*, i.e., potential associated genes/pathways that may explain how *ERG* functions in promoting PCa progression. Recently, several groups identified a prognostic gene signature that was able to reflect *ERG* status and was at some points, considered to be more robust than ERG itself, therefore reflecting downstream targets of ERG overexpression as summarized in Table 1 (Bismar et al. 2014; Barfeld et al. 2014; Gasi Tandefelt et al. 2013; Mochmann et al. 2014; Rajan et al. 2014; Setlur et al. 2008).

Other studies focused on identification of potential targets for *ERG*, which could act to explain disease progression or be of potential therapeutic targets. For example,

Table 1 *ERG*-related signatures and their predicted outcomes

Signature	Details	Signature development cohort	Testing of ERG status (yes/no)	Predicted outcome	Sources
Bismar et al.	*ERG*-like 10-gene expression signature	52 patients with castration-resistant disease	Yes	Aggressive features of ERG-mediated transcription	Bismar et al. (2014)
Barfeld et al.	33-Gene expression signature	19 samples (macro-dissected benign, primary, and metastatic PCa tissues)	Yes	Localized PCa and metastases	Barfeld et al. (2014)
Tandefelt et al.	36-Gene expression signature	48 *ERG*-positive primary PCa	Yes	Clinical outcome, cancer-specific, and overall survival	Gasi Tandefelt et al. (2013)
Mochmann et al.	8-Gene expression signature	50 lethal heavily pretreated CRPCs	Yes	A mesenchymal-like state associated with chemoresistance in leukemia cells	Mochmann et al. (2014)
Rajan et al.	7-Gene expression signature	Six patients with locally advanced/metastatic PCa	Yes	High-risk prostate cancer patients	Rajan et al. (2014)
Setlur et al.	87-Gene expression signature	455 *ERG*-positive, localized prostate cancer patients	Yes	Estrogen receptor (ER) signaling	Setlur et al. (2008)

TMRSS2-ERG gene fusion, combined with disrupted androgen receptor, induced the epigenetic regulators of transcription polycomb-group protein H3K27 methyltransferase EZH2-mediated repression of gene function to regulate PCa progression (Yu et al. 2010). Additionally, altered DNA methylation landscapes of polycomb-repressed loci were documented to be associated with PCa progression and *ERG* oncogene expression in PCa (Kron et al. 2013).

Genetic *ERG* knockdown in *TMPRSS2-ERG*-expressing PCa cells interfered with cell differentiation by repressing genes implicated in epithelial differentiation (*PSA* and *SLC45A3*/*Prostein*) and induced morphological changes; *ERG* knockdown also inhibited cancer cell growth in vitro and in mouse xenografts (Sun et al. 2008). Another study, using siRNA-treated cells, provided evidence that the activation of *C-MYC* oncogene was *ERG*-mediated (Sun et al. 2008). Reports also show that the *N-myc* downstream-regulated gene 1 (*NDRG1*) is fused to *ERG* in PCa (Pflueger et al. 2009).

The loss of homeodomain-containing transcription factor NKX3.1, a known prostate tumor suppressor, leads to epithelial cell overgrowth (Chen et al. 2002). Studies have established that loss of function of *NKX3.1* cooperates with the activation of *TMPRSS2-ERG* fusions in prostate tumorigenesis (Thangapazham et al. 2014). Defects of *NKX3.1*, such as allelic loss, haploinsufficiency, attenuated expression, or decreased protein stability, represent established pathways in prostate tumorigenesis that may be related to regulation by *TMPRSS2-ERG* fusion and *ERG* gene rearrangement (Chen et al. 2002). Another protein that is linked to *ERG* gene rearrangement and that represents a clinically relevant subgroup of prostate cancer is cysteine-rich secretory protein 3 (CRISP3) (Ribeiro et al. 2011; Grupp et al. 2013a; Al Bashir et al. 2014). It has been documented that CRISP3 expression was markedly increased in *PTEN*-deleted, *ERG*-positive tumors and that the combined status of *ERG*, *PTEN,* and *CRISP3* may be a strong predictor of PCA tumors with the worst outcome (Ribeiro et al. 2011; Al Bashir et al. 2014).

Recently, Gasi Tandefelt and colleagues reported on a 36-gene expression signature that identifies a subset within the *TMPRSS2-ERG* class of PCa that had a particularly poor clinical outcome (Gasi Tandefelt et al. 2013). These subsets of patients were characterized by tumor growth factor-β, signaling-dependent genes, leading to enhanced PCa progression. The proposed role of TGF-β in aggressive tumors is in line with other studies showing an important role for stromal cells and fibroblast to myofibroblast differentiation in tumor progression (Franco and Hayward 2012; Hagglof et al. 2014; Tidehag et al. 2014).

ERG linkage to phosphoinositol 3-kinase and AKT signaling

An early event in prostate cancers is the alteration of genes leading to inappropriate activation of the phosphoinositol-3 kinase/protein kinase-B (PI3K/AKT) signaling pathway (Li et al. 1997). This occurs most often through loss of function mutations or deletions of phosphate and tensin homologs on chromosome ten (*PTEN*), a lipid phosphatase that acts as a negative regulator of the PI3k/AKT signaling pathway (Li et al. 1997). Since *PTEN* loss is reported in a much larger percentage of HGPIN patients (Bettendorf et al. 2008), Carver and colleagues investigated the cooperative action of *PTEN* and *ERG* rearrangements (Carver et al. 2009). In a series of experiments combining human prostate cancer genetic assessment with transgenic mice, they showed that when *PTEN* loss occurs concomitantly with *ERG* aberrant expression, the role of *ERG* on cell migration and invasion rapidly promotes progression of HGPIN to invasive cancer (Carver et al. 2009). Loss of function mutations or rearrangements in the PTEN-associated protein, membrane-associated guanylate kinase inverted (MAGI), is also reported in prostate cancer (Mahdian et al. 2014). MAGI acts as a scaffold protein and augments the ability of *PTEN* to suppress AKT1 activation, and the loss of this protein would replicate the phenotype seen with *PTEN* loss. Although *ERG* has been shown to associate with *PTEN* genomic deletions, its clinical prognostic value has not been straightforward. An adverse outcome has been reported in tumors with combined PTEN loss and *TMPRSS2-ERG* rearrangement (Yoshimoto et al. 2008). Other studies suggested slightly better prognosis and documented that only *PTEN* deletions/decrease expression is of added adverse clinical outcome (Leinonen et al. 2013; Nagle et al. 2013). No matter the potential clinical implication, it is well established that *ERG*, *PTEN,* and *AR* are closely related and may reflect on molecular subtypes of PCa (Bismar et al. 2011; Bismar et al. 2012a).

ERG-related pathways and cellular responses

A clear picture of *ERG*-regulated genes in prostate cancer has not yet fully been elucidated. *ERG* overexpression in PCa cells in vitro conveys invasiveness and induces plasminogen activation, as well as matrix metalloproteinase pathways (Tian et al. 2014). Studies have noted that *ERG* modulates prostaglandin signaling in prostate cancer cells (Mohamed et al. 2011). A role for prostanoid signaling in enabling invasiveness of PCa has been shown, with the regulation of MMP2 and MMP9 proposed as the mechanistic basis for prostanoid regulation of tumor invasiveness

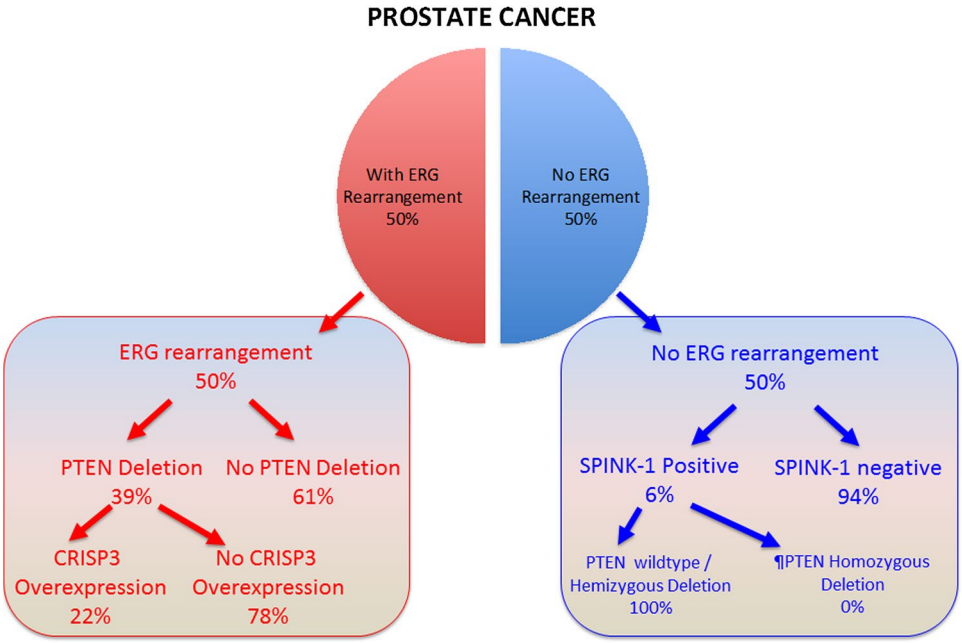

Fig. 1 Molecular classes and association of gene alterations in prostate cancer. Approximately 50 % of all prostate cancers show ERG gene fusion or other ETS gene rearrangement. In patients with positive ERG rearrangement, a concomitant deletion of PTEN and overexpression of CRISP3 lead to poor prognosis. In PCa with no ERG rearrangement, approximately 6 % show overexpression of SPINK1 that promotes metastatic disease. All of the SPINK1-overexpressing cells also showed PTEN deletion. SPINK1 overexpression has been reported in association within the same focus of PTEN homozygous deletions in nonlocalized PCa but not in localized disease

(Attiga et al. 2000). These data are in line with the long established observation of prostanoid and eicosanoid signaling being involved in the development of various carcinomas, including those of the prostate (Badawi 2000). In vitro overexpression of *ERG* is also reported to promote cell migration, a property necessary for tumorigenesis, without affecting proliferation and another member of the MMP family (Carver et al. 2009). A disintegrin and metalloproteinase with thrombospondin motifs 1 (ADAMTS1) (along with CXCR4) was found to be among genes strongly upregulated in the presence of *ERG* overexpression (Carver et al. 2009). Thus, regulation of the matrix metalloproteinase action in the tumor microenvironment is a likely consequence of *ERG* gene rearrangement.

Another protease pathway that is important in prostate cancer, but expressed markedly in *ERG*-negative cancers, is related to the serine peptidase inhibitor, Kazal type 1 (SPINK1). *SPINK1* encodes a 6-kDa trypsin inhibitor that is overexpressed in about 10–15 % of *ERG*-negative prostate cancers (Helgeson et al. 2008) and represents a subgroup of tumors positive for Trefoil3 (TFF3) (Terry et al. 2015). SPINK1 expression is also tightly linked to 6q15- and 5q21-deleted *ERG* fusion-negative prostate cancers, but was unrelated to PSA recurrence (Grupp et al. 2013b). *SPINK1* overexpression was associated with an aggressive subset of prostate cancer cell lines, and the genetic knockdown of SPINK1 attenuated the invasive phenotype and was further shown to mediate its oncogenic effects in part through epidermal growth factor receptor (*EGFR*) (Helgeson et al. 2008). Therefore, it was hypothesized that therapeutic targeting of either *SPINK1* or *EGFR* with monoclonal antibodies could suppress proliferation and invasion of prostate cancer cells (Ateeq et al. 2011). While previous clinical trials of anti-*EGFR* monoclonal antibody (cetuximab) in metastatic CRPC were disappointing, subsets of patients did show benefits and were likely a *SPINK1*-overexpressing patients (Slovin et al. 2009). There is now convincing evidence that *SPINK1* may be associated with increased risk of biochemical recurrence, and its inhibition is a promising therapeutic strategy (Terry et al. 2015; Leinonen et al. 2010).

Acetylation and deacetylation of core histones (H2A, H2B, H3 and H4) play a key role in epigenetic repression and are important for transcriptional regulation cell cycle progression and development (Ng and Bird 2000). Histone deacetylase 1 is a protein responsible for deacetylation of lysine residues on the core histones and serves an important role in the regulation of eukaryotic gene expression. Importantly, overexpression of HDAC1 is reported to induce angiogenesis by negatively regulating p53 and von Hippel-Lindau tumor suppressor genes (Kim et al. 2001; Ropero and Esteller 2007). Since HDAC1 is reported to be overexpressed in cancers with *ERG* rearrangement (Iljin et al. 2006), such regulation of tumor suppressor genes could represent another mechanism by which ERG rearrangements promote prostate cancer. One point in regard to *ERG* association with other molecular markers, mainly SPINK1, PTEN and CRISP3, is that a combination of two or more markers is likely to affect disease prognosis and may signify subclass of PCa depending on the site where they occur (Fig. 1). Lastly, a study has demonstrated that miR-221 downregulated in *TMPRSS2-ERG*-positive PCa cells, hence providing an evidence of the cross talk between *ERG* gene fusion and miRNA expression (Gordanpour et al. 2011).

Still, the molecular mechanisms underlying the expression of *ERG*-regulated genes remain to be investigated.

The diagnostic and prognostic value of *TMPRSS2-ERG* gene fusion

The diagnostic and prognostic value of ERG expression remains to be fully established. Several studies have examined the prognostic value of *TMPRSS2-ERG* fusion status in PCa. As summarized in Table 2, thirteen studies have shown a significant association between ERG fusion marker and PCa outcome. It is worth noting that although *TMPRSS2-ERG* has been frequently associated with poorer prognosis and more aggressive tumors, other studies have failed to show such prognostic value (Falzarano et al. 2010; Toubaji et al. 2011; Minner et al. 2011; Hoogland et al. 2012).

Mehra and colleagues identified *TMPRSS2-ERG* rearrangement to be associated with a high pathological grade in a cohort of 96 surgically treated patients (Mehra et al. 2007). However, Darnel et al. (2009) reported that *TMPRSS2-ERG* is more frequent in less aggressive tumors with Gleason grade 3. *TMPRSS2-ERG* gene fusion, ERG expression or composite intensity score was also identified as a prognostic factor of increased rates of biochemical recurrence and cancer-specific mortality in patients that had undergone surgical treatment for primary cancers (Nam et al. 2007a, b; Spencer et al. 2013). In another study, *TMPRSS2-ERG* gene rearrangement was associated with poor survival of prostate cancer patients with a combination of 5′ *ERG* deletion and *TMPRSS2-ERG* (25 % survival at 8 years), compared to patients negative for this rearrangement (90 % survival at 8 years) (Attard et al. 2008). Although, in another study assessing the gene fusion status in a cohort of patients managed expectantly, only 15 % of patients were found to have *TMPRSS2-ERG* rearrangement, this group of patients showed higher incidence of prostate cancer-specific death (Demichelis et al. 2007). This observation of less frequent *ERG* gene rearrangements in patients not managed surgically was validated in subsequent cohorts of patients with unsuspected, advanced, and castrate-resistant prostate cancer (CRPC) (Falzarano et al. 2010; Liu et al. 2011). Using ERG protein expression as a surrogate for *ERG* gene rearrangements in a cohort of men treated with hormonal therapy, we reported that high ERG intensity was associated with lower Gleason score, better response to hormonal therapy, better overall and cancer-specific survival, and longer free progression times to castration-resistant disease (Bismar et al. 2012b). In a revealing recent study, 1590 men with biopsy-diagnosed HGPIN, a precursor lesion of prostate cancer, showed that patients with ERG expression were more likely to develop prostate cancer (Park et al. 2014). While only 11.1 % of the HGPIN patients had *ERG* rearrangement, over a 3-year follow-up, 53 % of *ERG* rearrangement-positive patients and 35 % of *ERG*-negative patients progressed to prostate cancer, highlighting that HGPIN patient with ERG overexpression might need more rigorous clinical monitoring (Park et al. 2014).

However, as noted above, the data on the clinical significance of ERG are not all in agreement. Studies have demonstrated some contrasting results. Teng et al. (2013) showed that although there is significant association between ERG protein levels, extra-prostatic extension, and higher pathological stage, ERG progression is not associated with an adverse clinical outcome and is of limited prognostic value in localized prostate cancer. This was recently confirmed, using gene expression data to predict *ERG* status, where *ERG* was noted more often with lower grade Gleason scores and in association with extra-prostatic extension, but with no significant association to biochemical relapse (BCR) (Tomlins et al. 2015a).

Minner et al. (2011) showed no clinical difference between *ERG*-positive and *ERG*-negative PCa in the absence of antihormonal therapy. Hoogland et al. (2012) demonstrated that ERG expression by immunohistochemistry had no predictive value for prostate cancer recurrence or progression after radical prostatectomy and that increased ERG levels were associated with the upregulation of androgen receptor expression in clinical specimens. Furthermore, *TMPRSS2-ERG* fusion was found to be not prognostic for recurrence after radical prostatectomy for clinically localized prostate cancer, although men with *ERG* gene copy number gain without fusion were twice more likely to recur (Toubaji et al. 2011). When characterizing ERG in early onset PCa, ERG expression was noted to be present at higher rates of close to 60–65 % in two studies (Huang et al. 2014; Steurer et al. 2014). Furthermore, *ERG* was found to be associated with increased rates of biochemical recurrence postradical prostatectomy in one of those studies (Huang et al. 2014). In light of the contradictory results above, it seems that the significance of ERG expression in PCa is likely dependent on the heterogeneity of studied cohorts, the methods used to detect *ERG*, and the clinical outcome endpoint being investigated. For example, ERG expression shows a prognostic significance in localized prostate cancer in men below the age of 50 (Huang et al. 2014). Another study shows that *ERG* may also play a prognostic role in men treated expectantly by hormonal therapy or active surveillance (AS) as it reflects higher stage and higher tumor volume (Teng et al. 2013).

In a cohort of AS, positive *ERG* at diagnosis was suggested to be used to estimate the risk of progression during AS (Berg et al. 2014). *ERG* prognostic and diagnostic value in urine samples has been investigated and documented in

Table 2 Prognostic value of TMPRSS2-ERG rearrangements in selected studies

Biological characteristics	Method of detection	Cohort set	Clinical characteristics	Prognostic association/major findings	Sources
TMPRSS2-ERG through deletion	FISH	96	Surgically treated for clinically localized prostate cancer	*TMPRSS2* gene rearrangement was associated with high pathologic stage	Mehra et al. (2007)
TMPRSS2-ERG, any rearrangement	FISH	196	Treated by radical prostatectomy for localized PCa	*TMPRSS2-ERG* is more frequent in tumors with Gleason grade 3	Darnel et al. (2009)
TMPRSS2-ERG, any rearrangement	RT-PCR and direct DNA sequencing	26	Surgically treated for clinically localized prostate cancer (Gleason score 7)	Patients with the fusion protein had a significantly higher rate of recurrence	Nam et al. (2007a)
TMPRSS2-ERG, any rearrangement	RT–PCR and direct DNA sequencing	165	Surgically treated for clinically localized prostate cancer	Patients with the fusion protein had a significantly higher risk of recurrence	Nam et al. (2007b)
ERG expression	ERG immunohistochemistry (IHC)	100	Postradical prostatectomy	Patients with higher ERG expression intensity and composite scores were significantly more likely to develop biochemical relapse, metastases, and prostate cancer-specific mortality.	Spencer et al. (2013)
TMPRSS2-ERG through deletion	FISH	445	Patients who had been conservatively managed	Cancers lacking ERG alterations exhibited favorable cause-specific survival	Attard et al. (2008)
TMPRSS2-ERG through deletion	FISH and qPCR	111	Localized prostate cancers followed by expectant (watchful waiting) therapy	Fusion-positive prostate cancers may have a more aggressive phenotype	Demichelis et al. (2007)
TMPRSS2-ERG, any rearrangement	FISH	62	Patients with either transition or peripheral zone prostate cancer detected on radical prostatectomy	No significant correlation was found between fusion status and Gleason score or pathologic stage	Falzarano et al. (2010)
ERG expression	ERG immunohistochemistry (IHC)	312	PCa diagnosed in transurethral resection of the prostate	Low ERG intensity was significantly associated with higher GS	Bismar et al. (2012b)
ERG expression	ERG immunohistochemistry (IHC)	1590	Biopsy-diagnosed HGPIN	Patients with ERG expression were more likely to develop PCa	Park et al. (2014)
ERG expression	ERG immunohistochemistry (IHC)	198	Localized PCa	ERG expression was significantly associated with extra-prostatic extension and higher pathological stage	Teng et al. (2013)
ERG rearrangement	FISH	1577	From eight radical prostatectomy cohorts	m-ERG^{+} tumors were associated with lower preoperative serum prostate-specific antigen and Gleason scores, but greater extra-prostatic extension	Tomlins et al. (2015a)
ERG expression and *TMPRSS2-ERG* fusion	FISH and IHC	3261	Prostate cancer patients who had undergone radical prostatectomy	ERG expression was unrelated to clinical outcome and tumor phenotype	Minner et al. (2011)
ERG expression	ERG immunohistochemistry (IHC)	481	Patients treated by radical prostatectomy for prostate adenocarcinoma	ERG protein expression did not have prognostic value for the clinical end points	(Hoogland et al. 2012)

Table 2 continued

Biological characteristics	Method of detection	Cohort set	Clinical characteristics	Prognostic association/major findings	Sources
TMPRSS2-ERG, any rearrangement	FISH	344	172 cases (recurrence) and 172 controls (nonrecurrence) matched on pathological grade, stage, race/ethnicity, and age at the time of surgery	*TMPRSS2-ERG* fusion was not prognostic for recurrence after retro-pubic radical prostatectomy for clinically localized prostate cancer	Toubaji et al. (2011)
ERG expression	ERG immunohistochemistry (IHC)	121	Men diagnosed with localized PCa	Significant association between ERG expression and Gleason score and with biochemical relapse, but not with any other clinical pathologic parameter	Huang et al. (2014)
ERG expression	ERG immunohistochemistry (IHC)	265	Patients followed on AS	ERG expression is associated with increased risk of progression during active surveillance	Berg et al. (2014)

several studies to provide added value to serum PSA in detecting PCa and high-grade PCa in biopsies (Tomlins et al. 2015b). In summary, it is clearly established that *ERG* fusion marker is considered a key genomic marker and should be taken into consideration when the prognostic values of other genomic events are investigated.

Clinical utility of *TMPRSS2-ERG* gene fusion and *ERG* expression

Although PSA is still widely used to monitor PCa progression, it is too far from ideal to be considered as an early carcinogenic biomarker (Tomlins et al. 2005). It is noteworthy that PSA can early detect merely 23–44 % of PCa pathology (Draisma et al. 2009). Thus, it is mandatory, for the sake of better diagnostic sensitivity, to discover more efficient biomarkers. Consistent with this notion, Leyten et al. (2014) showed that *TMPRSS2-ERG* fusion, as a urinary biomarker, improves PCa detection and considerably reduces the frequency of unnecessary prostate biopsies. Furthermore, detection of *ERG* alterations is beneficial to determine the cancer origin and hence differentiate between aggressive PCa variants such as prostate small cell carcinoma from other small cell carcinomas with different origins (e.g., bladder or lung) (Guo et al. 2011). Recent works have introduced invaluable insights on using ERG as a therapeutic target. It has been demonstrated that either genetically knocking down *TMPRSS2-ERG* fusion or inhibiting its upstream signaling inhibits PCa growth (Wang et al. 2008; Dasgupta et al. 2012). A number of clinical trials are taking the advantage of the ability of *TMPRSS2-ERG* fusion product to exert tumorigenic activity, via its interaction with PARP1 [Poly (ADPRibose) Polymerase 1], to assess whether modulating this axis would benefit PCa patients (Brenner et al. 2011). Currently, ERG overexpression is considered a valuable tool in the diagnosis of PCa pathology.

Association and significance of *ERG* in radiation-treated patients

Data are mixed on the issue of ERG and radiosensitivity. An earlier study documented that *TMPRSS2-ERG* fusion-positive tumors were not more radiosensitive than the fusion-negative tumors and ERG rearrangement is therefore unlikely to be a predictive factor of image-guided radiotherapy response (Dal Pra et al. 2013). However, another study documented that patients with both *ERG* and *PTEN* genetic aberrations are at significant adverse BCR following brachytherapy (Fontugne et al. 2014). A previous study has shown the potential of ERG and PTEN to

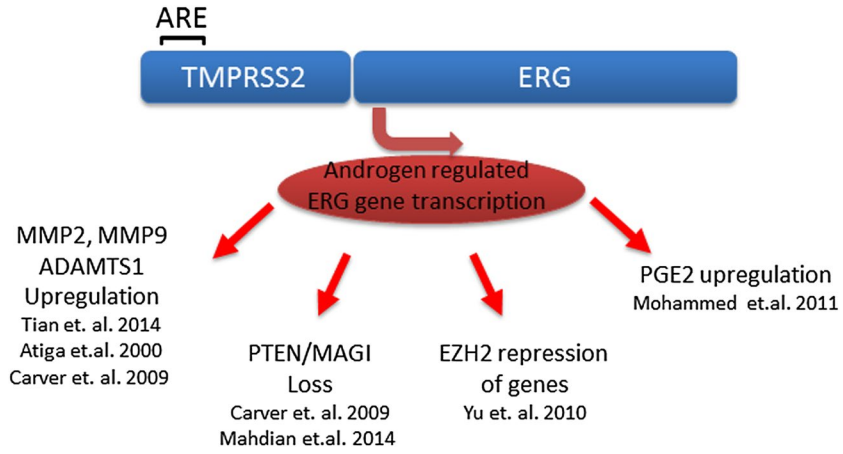

Fig. 2 Overview of mechanisms underlying ERG regulation in PCA. The most common ERG gene rearrangements involve fusion of exon 1 of TMPRSS2 with exon 4 or 5 of ERG. This leads to ERG becoming an androgen-responsive gene. Cellular function changes reported following such rearrangement include upregulation of MMPs, increased AKT signaling responses, EZH2 suppression of genes, and PGE2 upregulation-dependent PCa progression

assess the prognostic value in Brachytherapy patients, but these data require further validation (Fontugne et al. 2014). NKX3.1 haploinsufficiency is prognostic for prostate cancer relapse following surgery or image-guided radiotherapy (Locke et al. 2012). A recent study has shown that loss of *NKX3.1* promotes *TMPRSS2-ERG* fusion gene expression (Thangapazham et al. 2014), suggesting that the two molecular events may therefore be related. The full prognostic value in patients treated by radiotherapy still needs full exploration.

ERG and its potential diagnostic value in prostate pathology

ERG has been investigated in several studies as a diagnostic tool for prostate biopsies in conjunction with basal cell markers and AMACR (Shah et al. 2013; Yaskiv et al. 2011; Lee et al. 2014; Shah 2013). Specifically, it was assessed in atypical glands and suspicious foci (Shah et al. 2013). Overall, *ERG* is not a useful marker by itself to replace basal cell markers or AMACR, as it is expressed in only half of PCa as compared to AMACR, which is overexpressed in about 90 % of PCa (Yaskiv et al. 2011). *ERG* is thought to be more specific, but less sensitive as a diagnostic maker for PCa (Lee et al. 2015). The conclusion of these studies is that ERG, in combination with AMACR and basal cell makers, may offer added value in prostate biopsies, but the potential improvement in such a diagnostic test could be limited.

Conclusion

There is tantalizing evidence that ERG overexpression and *ERG* gene rearrangement is a useful predictive marker of metastatic potential or recurrence of prostate cancer. There is now a fairly good genetic and biological understanding of changes in prostate cancer. A number of clinical efforts to translate this knowledge to better diagnostic modalities and therapeutic strategies are underway. A key target is the rearrangement of the *ERG* gene and its interaction with other tumor-regulating pathways (Fig. 2). Further work to fully understand the functional consequence of these rearrangements and regulated cell signaling pathways promises exciting new advances in the diagnosis and management of prostate cancer.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare in this study.

Ethical approval NA (review article).

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