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Review

ERG-Mediated Cell Invasion: A Link between Development and Tumorigenesis

Alexandra M. Blee Haojie Huang

Department of Biochemistry and Molecular Biology, Mayo Graduate School, Mayo Clinic College of Medicine, Mayo Clinic, Rochester, Minn., USA

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Endothelial cells · Prostate cancer · Cell invasion · Gene fusion · ERG · TMPRSS2

Abstract
The transcription factor ERG is important during development for vasculogenesis and angiogenesis, blood vessel integrity, and maintenance of hematopoietic stem cells. In human adults, ERG is only expressed in endothelial cells and performs similar roles as in development to mediate blood vessel formation. However, aberrant overexpression of ERG in the adult contributes to diseases like prostate cancer, and the molecular and cellular mechanisms of ERG in tumorigenesis remain largely unclear. Studies of ERG-positive prostate cancers have shown that ERG promotes cell invasion and metastasis and contributes to poor patient prognosis. Together, these studies reveal ERG-mediated cell invasion as a potential link between normal ERG function in development and oncogenic ERG function in prostate cancer.

Introduction

ETS (E26 transformation-specific)-related gene (ERG) is a member of the ETS family of transcription factors. As a member of this family, ERG contains the conserved ETS DNA-binding domain, transcriptional activation and autoinhibitory domains, and a pointed (PNT) domain implicated in protein-protein interaction.

During development and in adult tissues, ERG is important for proper endothelial cell migration to form blood vessels. ERG directs the transcription of genes for endothelial cell differentiation, development of vasculature [1], and maintenance of hematopoietic stem cells

Dr. Alexandra M. Blee
Mayo Graduate School, Mayo Clinic College of Medicine
Guggenheim 13-28, 200 First Street SW
Rochester, MN 55905 (USA)
E-Mail blee.alexandra@mayo.edu

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[2]. In the absence of ERG, the endothelial cells in developing murine embryos are unable to migrate properly to form blood vessels, leading to severe developmental defects and embryonic lethality [3]. ERG is also expressed highly in the endothelial cells in mature adults and is essential for cell migration to form new blood vessels and maintain blood vessel integrity [4].

It is less clear how aberrant ERG overexpression in adult tissues can contribute to diseases such as prostate cancer, although this review will explore an emerging link between ERG-mediated cell migration and invasion in normal endothelial cells and prostate cancer cells. In adults, chromosomal rearrangement in the prostate between the androgen receptor-driven promoter of *TMPRSS2* and protein-coding regions of *ERG* can lead to abnormal expression of ERG in the prostate [5]. In this case, ERG is thought to cooperate with loss of tumor suppressor genes [6, 7], activation of oncogenes [8], changes in the epigenetic landscape [9, 10], and expression of genes that promote cancer [11], such as genes involved in cell invasion. Therefore, the role of ERG in cell migration seems conserved from endothelial cells to prostate cancer cells, where aberrant *ERG* expression cooperates with other genetic lesions to promote cancer cell invasion and metastasis as well as poor patient prognosis [11].

This review will provide a detailed summary of known biochemical functions of ERG and its well-established roles in endothelial cells and development, as well as current knowledge about the role of ERG in prostate cancer. Additionally, this review will focus on ERG-mediated cell invasion as a link between normal ERG function in endothelial cells and inappropriate *ERG* expression in adult tissues, particularly in the prostate. This link could provide researchers and clinicians with insights into therapy for advanced-stage, metastatic prostate cancer.

ERG Is a Member of the ETS Family of Transcription Factors

The first member of the ETS family of transcription factors, ETS-1, was identified in 1983 in chickens infected with acute avian leukemia retrovirus E26 [12, 13]. Subsequently, several other proteins with regions homologous to ETS-1 were characterized, including human ERG, first sequenced and characterized in 1987 by Reddy et al. [14]. ERG binds DNA in a sequence-specific manner via the ETS domain [15]. ERG also contains a PNT domain [16] and autoinhibitory regions [17], and regulates the transcription of target genes via a 47-amino acid C-terminal ETS transcriptional activation domain [18].

ETS Transcription Factors All Share the ETS Domain

The ETS domain contains approximately 85 amino acids and recognizes the purine-rich DNA sequence GGA(A/T) [15]. The ETS domain has a winged helix-turn-helix structure [17, 19]. Additionally, ERG has two autoinhibitory regions flanking the ETS domain: the N-terminal and the C-terminal inhibitory domain [17]. These inhibitory domains inhibit the activity of the ETS domain by decreasing the affinity of ERG for DNA, but they do not fully abolish the DNA-binding activity. Further molecular dynamics simulations show that the partial contact of DNA with autoinhibited ERG triggers a change in protein dynamics to fully relieve the autoinhibition [20]. However, this mechanism does not necessarily exclude the role of posttranslational modifications in regulating ERG DNA binding.

ERG Contains a PNT Domain That Is Also Present in a Subset of ETS Proteins

The ETS family members ERG, ETS-1, ETS-2, FLI1, GABPα, and TEL all share the PNT domain [16], which in ERG is composed of 4 well-structured core α-helices and a possible fifth, less-structured α-helix. The exact in vivo function of the PNT domain in ERG is unclear, but in other ETS proteins such as TEL, the PNT domain facilitates dimerization. In this case,

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TEL dimers have a higher affinity for DNA than TEL monomers [21]. Similar studies with ERG have shown that the PNT domain of ERG alone does not form dimers in solution [16]. However, others suggest that ERG may form dimers with itself or other ETS proteins when both the PNT and ETS domains are intact [22]. It is interesting to note that ERG dimers cannot bind DNA [22]; this is in contrast with the function of the PNT domain in TEL, where dimers bind DNA more strongly. More extensive study is required to determine whether the formation of ERG dimers in vivo via the PNT domain is a cellular mechanism that inhibits ERG.

Posttranslational Modifications of ERG Remain to Be Fully Characterized

Many ETS proteins are modified posttranslationally to regulate protein activity. For example, mitogen-activated protein kinases phosphorylate the ETS domain of ELK-1, which triggers ELK-1 DNA binding [23]. Recently, it was demonstrated that ERK2 phosphorylates serine 215 of ERG isoform 1 [24]. Although serine 215 is not localized in the ETS domain, this phosphorylation is essential for ERG binding to DNA, expression of its downstream target chemokine receptor CXCR4, and the aggressive behavior of prostate cancer cells [6, 24–26]. Other posttranslational modifications of ERG and their roles in protein activity or localization remain to be identified, which could shed light on the molecular mechanism of ERG-mediated transcription in prostate cancer.

Protein-Protein Interactions between ERG and Chromatin Modifiers or Other Transcription Factors Reveal Possible Mechanisms of Transcriptional Regulation

ERG can form homodimers, as well as heterodimers with other ETS family proteins including FLI1, ETS-2, ER81/ETV1, and PU.1 (encoded by *SPI-1*) [22]. Besides the ETS family member proteins, ERG can also interact with transcriptional coactivators or repressors. For example, the N-terminus of ERG interacts with the SET domain, bifurcated 1 protein (SETDB1, or ESET in mice), a histone H3 lysine 9 (H3K9)-specific histone methyltransferase [9, 27]. H3K9 methylation is recognized by the heterochromatin protein 1 (HP1) family proteins, resulting in gene silencing [28]. Additionally, SETDB1 can also suppress gene expression by recruiting other chromatin modifiers such as histone deacetylases 1 and 2 (HDAC1/2) and corepressors mSIN3A and B [10]. Intriguingly, HDAC1 is highly expressed in ERG-positive prostate cancer [29]. Therefore, the interaction of ERG with SETDB1 and subsequent recruitment of HP1 proteins, HDAC1/2, and mSIN3A/B represents an essential mechanism by which ERG mediates gene silencing.

ERG also interacts with activator protein 1 (AP-1), a heterodimeric transcription factor composed of FOS and JUN proteins [22]. Specifically, residues within helix α_3 of the ETS domain of ERG isoform 1 are involved in the interaction [30]. ERG-AP-1 heterodimers trigger activation of the collagenase 1 promoter and increase the production of matrix metalloproteinase (MMP) 1 protein [22, 31]. Conversely, ERG inhibits the stromelysin 1 promoter and prevents the production of MMP3 [31]. In the absence of ERG expression, another ETS protein (ETS-2) binds the stromelysin 1 promoter and activates transcription by recruiting FOS/JUN. When ERG is highly expressed, it binds to the DNA-binding domain of ETS-2 and inhibits the transactivation of this gene [32]. These studies demonstrate that ERG has a dynamic role in transcriptional regulation by either activating or silencing target gene expression.

It is worth noting that the findings described above have been validated by recent integrative mapping of transcription factor-transcription factor interactions [33]. The screening confirms that ERG interacts with ERG itself and other ETS members including FLI1, ETS-2, ER81/ETV1, PU.1, and JUN. It is also possible that more proteins will be identified that interact with and regulate the transcriptional activity of ERG in various cellular settings.

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ERG Function in the Normal Endothelium and Development

The role of ERG under normal physiological conditions during development is relatively well defined. Vertebrate *ERG* knockout models show defects very early in development, including a notable disruption of normal blood vessel formation. In human adults, ERG is normally expressed only in endothelial cells and regulates the formation of new blood vessels and maintenance of existing ones.

ERG Plays Well-Conserved Roles in Development, Particularly for the Vasculature of Developing Embryos

In mice, ERG is important for development of vasculature and hematopoiesis. Global deletion of mouse *Erg* exon 4, which contains a start codon for protein translation, resulted in a variety of vascular defects, and mice were embryonic lethal at E10.5-11.5 [3]. These defects include a reduced size of the embryo overall, hemorrhages in the head and trunk, widespread loss of blood vessels or lack of fusion between capillaries and larger vessels, pericardial effusions, and cardiac valve defects. This result is not unexpected, as the isoforms of ERG with a translation start codon in exon 4 are normally expressed in endothelial cells of mouse embryos [3]. The same study showed that ERG promotes expression of both *Snai1* and *Snai2* in the heart of E10.5 mice. SNAI1 and SNAI2 repress transcription of the vascular endothelial (VE)-cadherin gene and are important for the endothelial-to-mesenchymal transition during development, where endothelial cells lose strong cell-cell adhesions and adopt a migratory phenotype in order to form new vasculature [34]. Together, these findings suggest that if ERG and its downstream targets SNAI1 and SNAI2 are lost, endothelial cells will not migrate properly to form new vasculature. Additionally, endothelial cell-specific deletion of *Erg* in mouse embryos exhibits a very similar phenotype, including disorganization and decreased numbers of blood vessels, hemorrhages, defective heart development, and embryonic lethality by E10.5-11.5 [35]. In a third model, transactivation-deficient *Erg* homozygous mutant mice were embryonic lethal at E13.5, while the heterozygotes survived into adulthood [36]. The mutant ERG heterozygous adults had no immediately discernible phenotypes, but in bone marrow transplant assays, bone marrow from the heterozygotes was not able to support hematopoiesis in a normal host. Further study with the same model revealed that ERG is not required for the initial development of hematopoietic stem cells or initial hematopoiesis, but for definitive hematopoiesis to maintain the pool of hematopoietic stem cells [2].

Erg is also conserved in zebrafish, where it is involved in both vasculogenesis and angiogenesis of developing embryos. Beginning 12 h after fertilization, Erg is expressed in zebrafish embryos. Erg localizes to the primary vessel trunk along the midline of the embryo, smaller branching vessels, and angioblasts, where Erg upregulates genes required for angioblast proliferation and specification [37]. Overexpression of Erg in zebrafish induced an increased expression of vascular markers. Conversely, knockdown of *erg* in zebrafish resulted in no obvious phenotype. Moreover, when the second zebrafish ETS family gene *etsrp* was also targeted along with *erg*, the embryos displayed decreased vessel development. These observations suggest that the role of Erg in zebrafish vascular development can be compensated for by other proteins such as Etsrp [37].

ERG in Adult Endothelial Cells

In humans, ERG regulates the transcription of genes important for cell survival, vessel integrity, cytoskeleton dynamics, and cell migration (fig. 1a). Compared with the majority of other tissue types, ERG is only expressed in mammary artery, coronary, and venous endothelia [1] as well as human umbilical vein endothelial cells (HUVECs) [38]. In these cells, an endothelial cell-specific promoter and general transcriptional machinery likely regulate *ERG*

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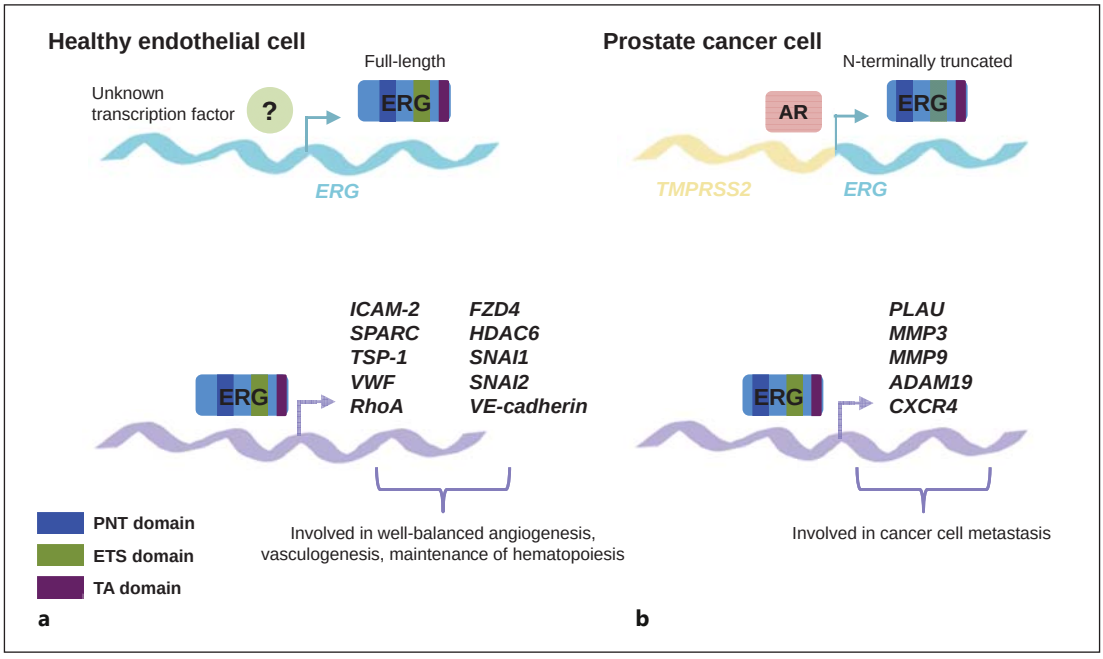

Fig. 1. Transcriptional regulation for cell migration and invasion in healthy endothelial cells and prostate cancer cells. **a** In healthy endothelial cells, *ERG* is transcribed at relatively high levels through an unknown mechanism. Highly expressed ERG protein in turn regulates the transcription of genes important to maintain well-balanced endothelial cell migration during the development of vasculature. **b** In prostate cancer cells, *ERG* is transactivated by androgen receptor (AR) as the result of aberrant gene fusion with *TMPRSS2*. Overexpressed ERG in turn regulates the transcription of genes related to cell invasion and tumor metastasis.

expression, although this is currently unknown. Many studies focus on the mechanisms of ERG function in the commercially available HUVECs.

HUVECs without ERG lose the ability to form new blood vessels from preexisting vasculature and undergo programmed cell death [4]. Several molecular changes occur in cells upon losing ERG. Because ERG interacts directly with the VE-cadherin promoter to initiate transcription of VE-cadherin in HUVECs, cells without ERG also lose VE-cadherin expression [4]. Normally, VE-cadherin spans the cell membrane and binds homotypically between neighboring cells, while β-catenin links the intracellular portion of VE-cadherin to the actin cytoskeleton. Both VE-cadherin and β-catenin are required for junctional integrity between endothelial cells in blood vessels, as well as for regulation of permeability [4]. In addition, β-catenin is an essential component of Wnt signaling that triggers the transcription of target genes that are largely involved in cell differentiation, proliferation, and self-renewal. In the absence of Wnt signaling, free β-catenin is rapidly degraded [39]. Interestingly, ERG can also activate the transcription of frizzled-4 (FZD4) receptor, a key receptor in the Wnt pathway [35]. Therefore, without ERG, HUVECs are unable to maintain proper cell-cell junctions due to loss of VE-cadherin, FZD4, and β-catenin. This mechanism not only highlights the importance of ERG in developing vasculature, but also explains the extreme phenotypes caused by ERG loss in HUVECs, including apoptosis, loss of blood vessel integrity, and the developmental defects observed in other species.

In a comprehensive differential gene expression study, RNAi knockdown of *ERG* changed the expression of nearly 500 genes in endothelial cells [40]. This study confirmed that ERG drives the basal expression of intracellular adhesion molecule (ICAM)-2, a constitutively expressed cell-cell adhesion molecule in endothelial cells [41]. In addition, this study iden-

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tified 4 new target genes activated by ERG: von Willebrand Factor *(VWF)*, which negatively regulates angiogenesis [42]; secreted protein acidic and rich in cysteine *(SPARC)*, which also negatively regulates angiogenesis [43]; thrombospondin-1 *(TSP-1)*, another inhibitor of angiogenesis [44], and *RhoA*, which regulates actin cytoskeleton dynamics [45]. It remains unclear why ERG overexpression has been linked with aggressive prostate cancer; yet these downstream targets of ERG inhibit angiogenesis. The specific tissue microenvironment could help explain this paradox. It is also possible that normal angiogenesis is not a linear pathway but requires a balance between positive and negative feedback in order to function properly. While the mechanistic details remain to be elucidated, ERG clearly plays a crucial role in the development and maintenance of vasculature.

ERG also directly regulates HDAC expression in endothelial cells to regulate tubulin stability and dynamics. ERG activates the transcription of HDAC6, a cytosolic protein that deacetylates tubulin [46]. Ultimately, endothelial cells with high *ERG* expression also have high expression of *HDAC6*, which leads to tubulin deacetylation and microtubule destabilization, cortactin deacetylation, increased actin dynamics, and increased cell migration (which also contributes to increased angiogenesis) [46]. These data also support ERG as a crucial factor for endothelial cell migration and angiogenesis.

Aberrant Expression of *ERG* Promotes Tumorigenesis

ERG Is Aberrantly Expressed in Sarcoma, Leukemia, and Prostate Cancer

Although this review focuses on ERG overexpression specifically in prostate cancer, it is important to note that ERG has an established oncogenic role in multiple cancer types. In both Ewing sarcoma and myeloid leukemia, ERG is aberrantly overexpressed due to gene fusions. In Ewing sarcoma, the *ERG* gene is fused with the *EWS* gene (also known as Ewing sarcoma RNA-binding protein 1 or *EWSR1*) through a chromosomal rearrangement [47]. In myeloid leukemia, a fusion occurs between *ERG* and *TLS/FUS*, which encodes an RNA-binding protein with 56% homology to EWS. This fusion is thought to be important for cell transformation, similar to *EWS/ERG* [48].

In prostate cancer, ERG overexpression also results from a chromosomal rearrangement (fig. 1b). Tomlins et al. [5] first characterized a chromosomal rearrangement and gene fusion event in approximately 50% of prostate cancers that results in overexpression of ERG. This event has been linked with progression and advanced stage of prostate cancer as well as poor patient survival, compared to prostate cancers lacking the rearrangement [49]. The rearrangement occurs most commonly between *TMPRSS2* (an active, androgen receptor-driven transmembrane serine protease gene) and *ERG*. In this rearrangement, the promoter and a noncoding portion of *TMPRSS2* are fused to the coding region of *ERG*. Because the androgen receptor can activate the expression of *TMPRSS2*, this gene fusion event results in the expression of ERG protein (usually of N-terminally truncated ERG, due to imprecise joining) [5]. In addition, another ETS family gene, *ETV1*, is also fused with *TMPRSS2*, but less frequently [5]. ETV1 and ERG overexpression in prostate cancer appears mutually exclusive, where perhaps a redundancy between ERG and ETV1 prevents transformed cells from acquiring overexpression of both [5]. Many ETS family members have a similar structure and function, including ERG and ETV1, although it is important to note that one structural difference between ERG and ETV1 is the absence of the PNT domain in ETV1.

There are several possible mechanisms for the gene fusion event that vary depending on the tumor and the exact cell within the tumor. For *ETV1* (7p21.2) overexpression in prostate cancer, the initiating event is usually a true chromosomal translocation [5]. Similarly for *ERG*, a chromosomal translocation will result in fusion of *TMPRSS2* and *ERG*. Because these two

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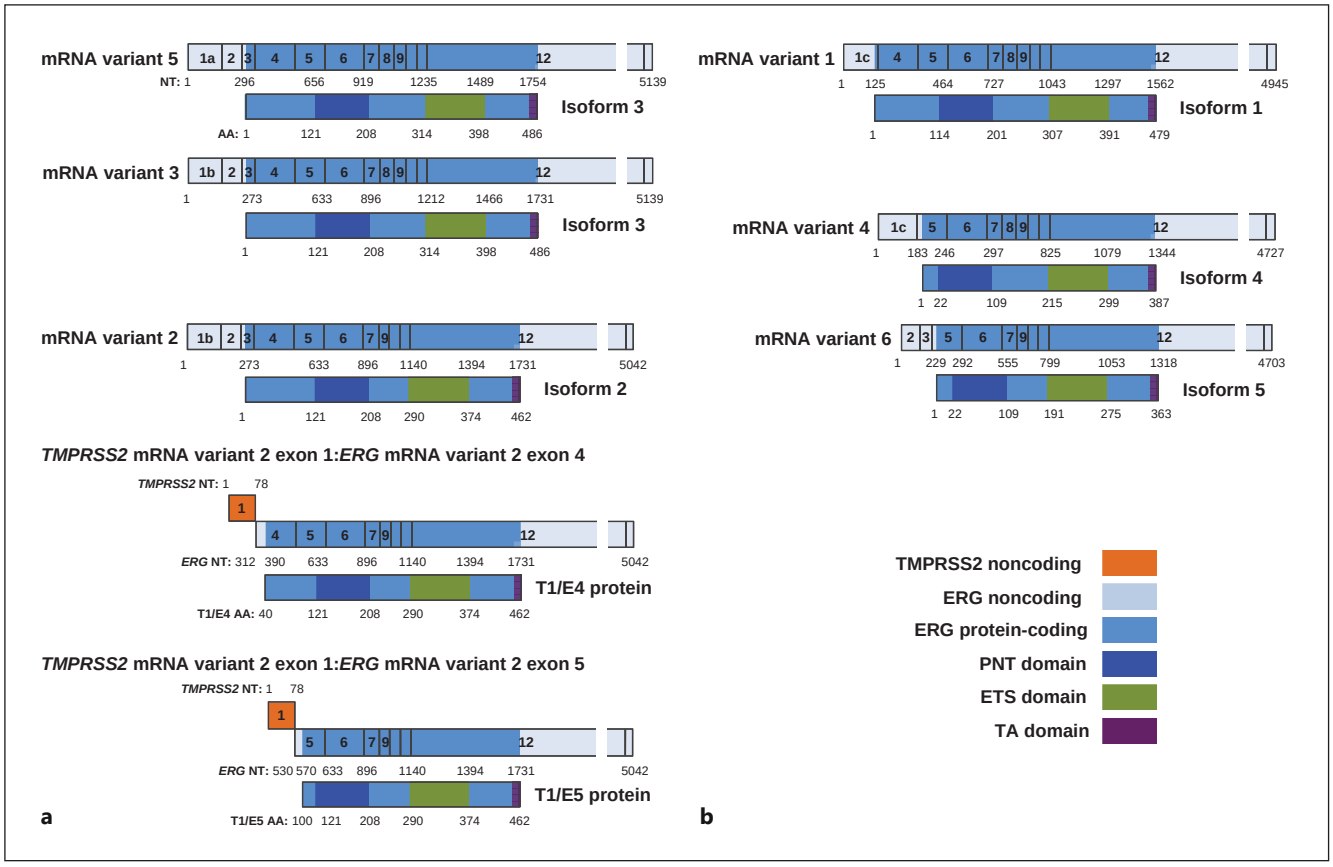

Fig. 2. mRNA transcript variants and corresponding protein isoforms of wild-type and prostate cancer-associated, truncated forms of *ERG*. Exon and protein domain maps of the *ERG* variants that share intact PNT, ETS, and TA domains. Exact residues defining the PNT domain are uncertain; the structured region begins at residue 124 of variant 1 [16], but ERG may contain a relatively unstructured fifth N-terminal α-helix at residue 114. Autoinhibitory regions [17] are not diagrammed, due to alternative splicing of exons between the PNT and ETS domains. **a** Protein isoform 3 is the canonical protein sequence for ERG, encoded by both mRNA variants 5 and 3. mRNA variant 2 encodes protein isoform 2, which is also the isoform most commonly found in prostate cancer fused with *TMPRSS2*. *TMPRSS2* transcript variant 2 exon 1 (T1) and *ERG* transcript variant 2 exon 4 (E4) or exon 5 (E5) form the most common fusions in prostate cancer. These proteins are translated beginning at ERG isoform 2 amino acid 40 (for E4) or amino acid 100 (for E5). T1/E4 and T1/E5 share intact PNT, ETS, and TA domains. **b** Maps for two other subgroups of *ERG* variants, with increasingly truncated N-termini. All nucleotide sequences were accessed through NCBI: *ERG* mRNA variant 1 NM_182918.3, variant 2 NM_004449.4, variant 3 NM_001136154.1, variant 4 NM_001136155.1, variant 5 NM_001243428.1, and variant 6 NM_001243429.1; *TMPRSS2* mRNA variant 2 NM_005656.3. The exact locations of gene fusions have been described previously [7, 52]. ETS domain sequence: [15]; PNT domain sequence: [16]; TA domain sequence: [18]. NT = Nucleotide; AA = amino acid.

genes are located on the same arm of chromosome 21, a deletion of the region between *TMPRSS2* (21q22.2) and *ERG* (21q22.3) can also result in fusion [50]. Previous studies suggest a role for chromodomain helicase DNA-binding protein 1 (CHD1) in the formation of the rearrangement. CHD1 binds to H3K4-trimethylated histones and remodels chromatin with high levels of this transcriptionally active histone mark. In prostate cancer, *CHD1* is often deleted or mutated, and, intriguingly, the *CHD1* loss is only detected in ERG-negative prostate cancers [50, 51]. Mechanistic studies suggest that chromatin remodeling mediated by CHD1 allows the activation of androgen receptor target genes such as *TMPRSS2*, and that consistently open

chromatin at these loci increases the likelihood of chromosomal breaks and induces rearrangements that could produce aberrant gene fusions [51].

Because the rearrangement events do not always occur in exactly the same manner, there are many different *TMPRSS2-ERG* fusion variants expressed in prostate cancer (fig. 2). The fusions occur between *TMPRSS2* exon 1 or 2 and *ERG* exon 2, 3, 4, or 5 (referred to as T1/E2, T1/E3, etc.), with T1/E4 and T1/E5 occurring most commonly [11, 52]. Exons 1 and 2 of *TMPRSS2* do not encode protein, while *ERG* exons 4 and 5 do encode protein. Therefore, for the majority of *TMPRSS2-ERG* fusions, the active *TMPRSS2* promoter drives the expression of N-terminally truncated ERG, and no true fusion protein product is translated for both T1/E4 and T1/E5. Although T1/E4 and T1/E5 are truncated proteins, both of them contain the known functional domains, including the ETS, PNT, and transactivation (TA) domains [11]. Of the different *ERG* transcript variants, *ERG* variant 2 is most frequently fused with *TMPRSS2* [53]. It is also interesting to note that in prostate cancers with ERG overexpression, the N-terminus of ERG is usually lost. However, because T1/E4 and T1/E5 contain the known functional domains, it is likely that these fusion variants all maintain the same ability to activate transcription. In contrast, these truncated isoforms may exhibit different gene silencing abilities. As mentioned above, the N-terminus of ERG interacts with the histone methyltransferase SETDB1 to silence genes [27]. Thus, it is conceivable that the N-terminally truncated ERG protein encoded by *TMPRSS2-ERG* fusions in prostate cancer could lose its gene silencing function. Future investigation in this direction is warranted. Finally, a recent study shows that the N-terminus of ERG contains a degron motif recognized by the E3 ubiquitin ligase SPOP and that N-terminally truncated ERG proteins in prostate cancer evade SPOP-mediated protein degradation [54].

ERG Overexpression Cooperates with Tumor Suppressor Loss and Oncogene Gain to Promote Prostate Cancer Progression

Several studies have shown that the *TMPRSS2-ERG* fusion is present in an early precancerous stage called prostatic intraepithelial neoplasia, particularly in those adjacent to cancerous tissues [6, 7, 11]. Whether or not the fusion event is truly a driving mutation for prostate tumorigenesis remains elusive. Previous studies show that additional genetic lesions, such as loss of the tumor suppressor PTEN, are necessary to induce prostatic intraepithelial neoplasia lesions and cancer in mice overexpressing ERG [6, 7, 55, 56]. Moreover, ERG may contribute to prostate tumorigenesis via transactivation of c-MYC, an oncoprotein relevant to prostate cancer [8]. Collectively, these studies suggest that the fusion event occurs relatively early during prostate oncogenesis, but this fusion is likely accompanied by other cooperative mutations that advance the disease. More research is necessary to fully understand the role of ERG in cancer development and progression.

One well-documented outcome of ERG overexpression in prostate cancer is increased cell invasion (fig. 1b). This may contribute to worse patient prognosis, although the correlation has not been convincingly validated by large patient cohort studies [11]. ERG overexpression increases invasion in mouse models of ERG-positive prostate cancer, in the prostate cancer VCaP cell line with endogenous T1/E4, and nontransformed RWPE and PrEC cell lines transiently transfected with truncated *ERG* [56]. ERG overexpression in both VCaP cells and ERG-positive RWPE cells induced an increased expression of MMP genes *MMP3*, *MMP9*, and *ADAM19* as well as plasminogen activator pathway genes *PLAU* and *PLAT*. Interestingly, inhibition of the plasminogen activator pathway was found to decrease cell invasion, while inhibition of MMPs had no effect on cell invasion [56], suggesting the plasminogen activator pathway is most important for prostate cancer cell invasion. The plasminogen activator pathway is a well-established component of both endothelial cell migration and cancer cell invasion [57]. Urokinase-type plasminogen activator (uPA) is encoded by *PLAU* and secreted

by cells, where it is confined to the cell-extracellular matrix boundary by uPA receptor (uPAR). Once bound by uPAR, uPA cleaves inactive plasminogen, resulting in active plasmin, another serine proteinase. Plasmin cleaves many extracellular matrix proteins, including fibronectin, vitronectin, and fibrin, to allow cells to migrate through the matrix [57]. ERG also binds the osteopontin *(OP)* gene promoter to activate the transcription of *OP*, the expression of which has been linked to activation of MMPs and uPA, tumor cell invasion, and metastasis [58]. This role of ERG in prostate cancer cell invasion and ERG-mediated expression of MMPs and plasminogen activators is comparable with normal ERG function in endothelial cells, where cells migrate through surrounding tissues and degrade the extracellular matrix as they generate new blood vessel tracks.

Another link between normal ERG-mediated cell migration in vascular development and prostate cancer cell invasion is the expression of CXCR4 [6], a chemokine receptor that is commonly expressed in endothelial cells and cancer cells [59]. In ERG-positive cancers, ERG binds to the promoter of *CXCR4* to activate transcription [25, 26]. Several studies have demonstrated functional outcomes of ERG-mediated CXCR4 overexpression, including increased cell migration [6] and metastasis to bone [25]. Because the CXCR4 ligand, CXCL12, is secreted by bone stromal cells, CXCR4 expression serves as a mechanism to attract circulating ERG-positive prostate cancer cells to bone [25]. CXCR4 expression in prostate cancer provides an interesting link to normal ERG function in endothelial cells, where CXCR4 is important for endothelial cell precursors in angiogenesis to direct the migration of endothelial precursors along CXCL12 gradients [59].

Concluding Remarks

This review has discussed functional connections between ERG overexpression in prostate cancer and the normal developmental roles of ERG. These insights begin to explain how normal functions of ERG in endothelial cells and development can be detrimental in an inappropriate temporal and spatial setting such as the adult prostate. Although the exact genes regulated by ERG in the prostate versus in endothelial cells or development have not been compared in a pairwise manner, many of the underlying mechanisms seem conserved. In particular, ERG has a role in cell invasion that is important for both the development of new blood vessels and metastasis of cancer cells. A better understanding of this ERG-mediated cell invasion in prostate cancer may lead to the identification of new therapeutics.

Despite the progress made in identifying ERG overexpression in approximately half of all prostate cancers and several specific downstream consequences, there are many remaining gaps in our knowledge of ERG functions in both cancer and development. Upcoming areas of study may include defining the mechanism for ERG-mediated transcription in the prostate, including the identification of binding partners of ERG that can activate or inhibit ERG-mediated gene transactivation, components of the general transcriptional machinery that interact with ERG, and the regulation of ERG functions by posttranslational modifications. Additionally, understanding the regulation of ERG in healthy, noncancerous endothelial cells, where ERG is expressed at relatively high levels yet does not promote cancer, may provide therapeutic options to selectively turn off the oncogenic functions of ERG in the prostate.

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Disclosure Statement

The authors declare no conflicts of interest.

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