ETS transcription factors and prostate cancer: The role of the family prototype ETS-1 (Review)

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Abstract. The ETS family of transcription factors is known to play important roles in various biological processes such as development, differentiation, proliferation, apoptosis, migration, tissue remodeling, invasion and angiogenesis in various cell types including B cells, endothelial cells, fibroblasts as well as diverse neoplastic cells. In prostate cancer, recurrent gene fusions involving members of the ETS family are frequently reported. ETS-1, the prototype of the ETS family, is expressed in different cell types and is known to play various roles during both physiological and pathological conditions. In this review, we focus on studies investigating the role of ETS-1 in prostate cancer.

Contents

1. Introduction

The *ETS-1* gene was first identified as the cellular proto-oncogene of the retroviral v-*ETS* oncogene that is associated with v-*MYB* in the avian leukemia retrovirus E26 (E twenty-six-specific, *ETS-1*) (1-3). ETS-1 is expressed in different cell types and is reported to play various roles during physiological (e.g., embryonic development, lymphoid differentiation, vascular development, hematopoietic differentiation), as well as pathological conditions (reviewed in refs. 4,5). ETS-1 is implicated in tumor vascularization and angiogenesis, as well as in contributing to tumor proliferation and invasion by acting within both neoplastic cells and fibroblasts of the tumor stroma (6-15).

ETS-1 is highly conserved among species, and is considered to be the prototype and the founding members of the *ETS* gene family of transcription factors (16-18). The ETS family of transcription factors is characterized by an evolutionary highly conserved DNA-binding domain, the ETS domain, which consists of about 80 amino acids with 4 tryptophan repeats that recognizes DNA sequences containing a GGAA/T core motif (reviewed in refs. 5,19). Phylogenetic analysis of the ETS domain identified subfamilies of more highly related members (20). Different ETS members have various functions which may be due to their binding preferences for distinct flanking sequences that could facilitate their binding specificity (20). Moreover, overlapping functions of ETS members, as well as redundant occupancy at proximal regulatory gene regions have been reported (20,21). Therefore, trans-activation or trans-repression of genes could be determined by the dynamic binding equilibrium, the activity of the ETS trans-activation domains, as well as the ternary complex formation of different ETS members and other transcription factors (22).

In humans, the ETS family consists of 27 members (23) and is known to play important roles in a wide range of processes (e.g., development, differentiation, proliferation, apoptosis, migration, tissue remodeling, invasion and angiogenesis) in different cell types such as B cells, endothelial cells, fibroblasts and neoplastic cells (24-29).

2. ETS gene fusions in prostate cancer

Recurrent gene fusions between the androgen-regulated prostate-specific serine protease *TMPRSS2* gene, and several members of the ETS family of transcription factors (*ETV-1, ETV-4, ETV-5*, and most commonly *ERG*) are frequently found in prostate cancer (reviewed in refs 30-32). Such translocations lead to increased expression of the rearranged ETS members in response to androgens (reviewed in ref. 31). Some studies have suggested that ETS rearrangements are sufficient for initiation of prostate neoplasia, while other studies have indicated that the rearrangements may foster progression rather than initiation events in prostate tumorigenesis (33,34).

While the *TMPRSS2-ERG* fusions are the most predominant in prostate cancer (15-80%), other rare ETS gene rearrange-

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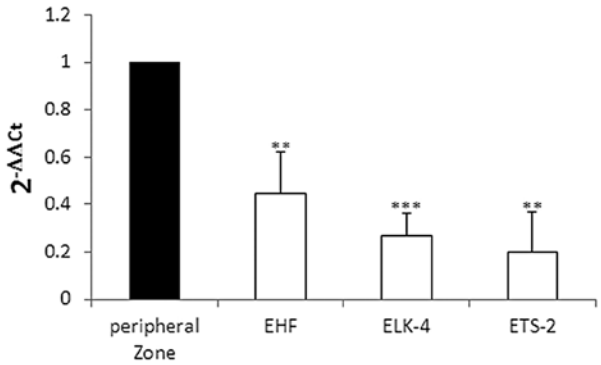

Figure 1. Expression analysis of the ETS-family members in prostate cancer tissues. Expression pattern of all 27 ETS transcription factors by quantitative RT-PCR (qRT-PCR) using RNA extracted from laser microdissected glands of the normal prostate proper (or the peripheral zone) and tumor glands. EHF, ELK4, and ETS2 show significant down-regulation in the tumor glands compared to the normal glands. Significance was calculated with the Student's t-test. P-values are indicated as $^{***}P<0.001$, $^{**}P<0.01$ and $^{*}P<0.05$ (45).

ments involving primarily *ETV-1*, as well as *ETV-4* and *ETV-5* constitute approximately 1-10% of cases (reviewed in refs. 31,32,35). Notably, investigations of the ERG rearrangement in both primary prostate cancer and metastases have suggested that the ERG rearrangement status is a clonal expansion event during prostate cancer progression (36-39).

Several studies have been undertaken to understand the role of these *ETS* genes and fusions in prostate cancer (33,40-43). For instance, knockdown of *ERG* in prostate cancer cell lines was reported to induce morphological changes and to lead to the inhibition of cell growth in both cell culture and mice, whereas overexpression of *ERG* leads to an increase in cell invasion (40). Moreover, overexpression of TMPRSS2-ERG in primary or immortalized benign prostate epithelial cells was able to induce invasion, but unable to increase proliferation or anchorage-independent growth (reviewed in ref. 41). Studies investigating the role of ETV-1 have shown that ETV-1 inhibition in prostate cancer cells leads to a reduction in invasion (44), while overexpression results in an increase in cell invasion (33). Other studies examining the roles of ETV-4 and ETV-5, have shown that ETV-4 is required for anchorage-independent growth and cell proliferation gene expression program in prostate cancer cell lines (42), whereas ETV-5 ectopic overexpression in benign prostate cells induces invasion (43).

3. Expression of the ETS family in prostate cancer

The expression of some of the ETS family members in prostate cancer tissues was reported using immunohistochemistry, RT-PCR, microarrays, and/or *in situ* hybridization (reviewed in ref. 41). Some of the *ETS* genes such as *ETS-1, FLI1, ERG, ELF-1* and *PDEF* were found to be overexpressed in tumors, while others such as *ETV-4* and *ELK-1* were reported to show negative staining in prostate cancer tissues (reviewed in ref. 41).

In order to have a complete analysis of the expression of the *ETS* family members in prostate cancer, we have recently reported the expression pattern of all 27 ETS transcription factors by quantitative RT-PCR (qRT-PCR) using RNA extracted from laser microdissected glands of the normal prostate proper (or the peripheral zone) and moderately differentiated tumor glands from patients who had undergone radical prostatectomy (Fig. 1) (45). Our analysis revealed that only 3/27 ETS family members, *EHF, ELK-4* and *ETS-2* exhibit significant differences in expression between normal and tumor glands (Fig. 1).

In a subsequent study using a larger number of patients which included both moderately and poorly differentiated tumor glands, we examined by qRT-PCR the expression of the *ETS* gene *ERG* and that of *TMPRSS2* in the moderately/poorly differentiated tumor glands compared to normal glands (46), as recurrent gene fusions between *TMPRSS2* and *ERG* are the most commonly found ETS gene fusions in prostate cancer (15-80%) (reviewed in refs. 30-32). Our study revealed the up-regulation of both *ERG* and *TMPRSS2* in tumor glands compared to the corresponding normal glands (Fig. 2) (46) which supports previous reports (41).

In parallel with investigating the expression pattern of the *ETS* family in prostate cancer tissues, we examined the expression pattern of all 27 *ETS* members using qRT-PCR in the androgen-sensitive VCaP and LNCaP, and the androgen-insensitive PC3 and DU-145 prostate cancer cell lines (45). We found a unique expression pattern of the *ETS* family members among the four cell lines (Fig. 3).

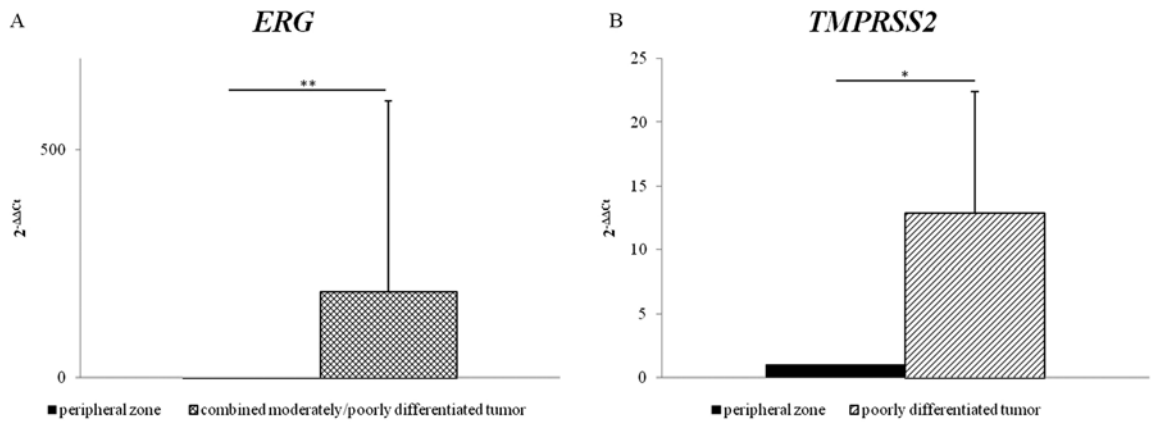

Figure 2. Expression of *ERG* and *TMPRSS2* in lasermicrodissected glands of the prostate proper and in prostate carcinoma glands. The relative expression of *ERG* (A) and *TMPRSS2* (B) was measured by quantitative RT-PCR in prostate carcinoma glands compared to normal glands of the prostate proper. Significance was calculated with the Student's t-test. P-values are indicated as $^{***}P0.001$, $^{**}P<0.01$ and $^{*}P<0.05$ (46).

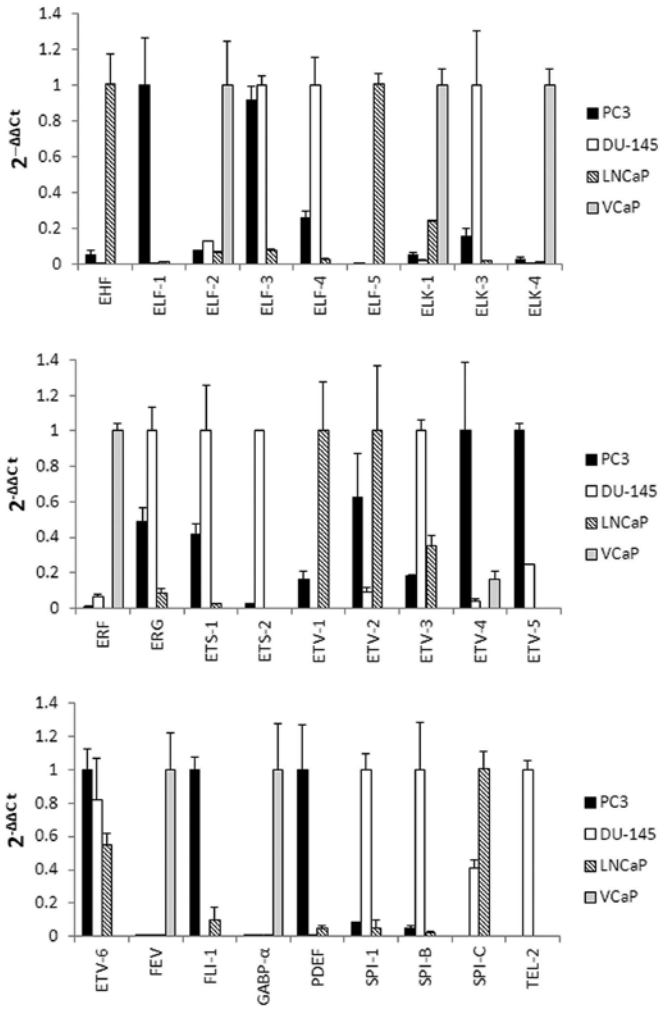

Figure 3. Expression profiles of ETS family members in prostate cancer cell lines. The expression of the 27 ETS family members was measured by qRT-PCR in LNCaP, VCaP, PC3 and DU-145 prostate cancer cell lines (45).

The expression level of a given *ETS* family member in each of the cell lines may reflect the unique role that ETS member plays in that particular cell line. Another plausible explanation for the differences in the expression pattern of the ETS family members among the four cell lines may be due to the distinct biological properties of each cell line, as each cell line was derived from a different origin (45). For instance, DU-145 cells were derived from a brain metastasis, PC3 cells from an advanced androgen-independent bone metastasis, LNCaP cells from a supraclavicular lymph node metastasis, and VCaP cells from a metastatic lesion to a lumbar vertebral body of a patient with hormone refractory prostate cancer (45).

Finally, the role of the *ETS* genes, *EHF, ETS-2* and *ERG* which we have identified in prostate cancer tissues (45,46), have been investigated in prostate cancer cell lines (40,47-49). Knockdown of EHF in prostate cancer cell lines has been shown to inhibit cell proliferation and to induce a premature cellular senescence (47). Studies investigating the role of ETS-2 have reported that blockade of ETS-2 function reduces transformed properties of prostate cancer cells (48), and down-regulation of ETS-2 expression leads to growth inhibition and apoptosis in prostate cancer cells (49). Lastly, knockdown of *ERG* was reported to induce morphological changes and result in cell growth inhibition in both cell culture and mice, whereas over-expression of *ERG* resulted in an increase in cell invasion (40).

4. The roles of the ETS-family prototype ETS-1 in prostate cancer

As mentioned in the previous section, ETS-1 is expressed in different cell types and is reported to play various roles during both physiological and pathological conditions (reviewed in refs. 4,5).

In prostate cancer, ETS-1 has been reported to be overexpressed in latent and clinically manifest carcinomas and a strong expression of ETS-1 has been associated with poor tumor differentiation (12). Additionally, we have recently reported that *ETS-1* is up-regulated in prostate carcinoma glands compared to normal glands (50).

As ETS-1 has been shown previously to promote proliferation, migration and invasion in different neoplastic cells such as melanoma, HeLa and glioma cells (26-28), we have recently examined whether ETS-1 has a similar effect upon these biological properties in prostate cancer cells (29). We established two stable PC3 prostate cancer cell line cultures by transfection with

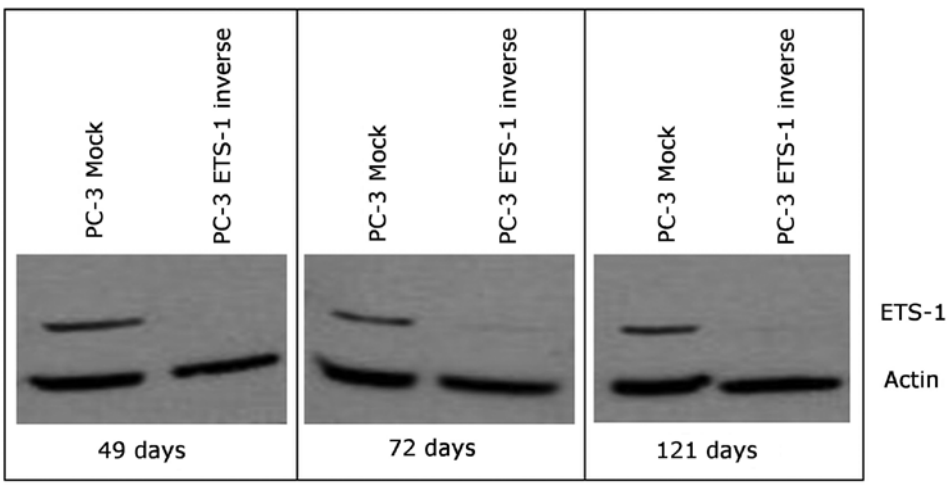

Figure 4. Stable transfection of ETS-1 in PC3 cells. Western blot analysis showing stable transfection over a period of 121 days of PC3 cells with an empty plasmid (mock) and a plasmid carrying ETS-1 inverse (29).

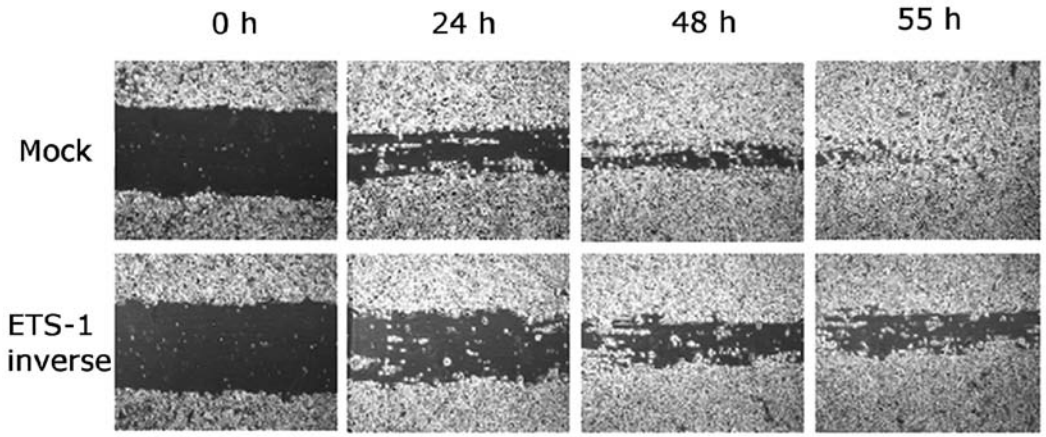

Figure 5. Wound assay: effects of ETS-1 on cell migration. Monolayers of confluent cultures were lightly scratched with a pipette tip and phase contrast images of cultures were taken immediately after wounding (0 h) and after 24, 48 and 55 h. Wounds were almost completely colonized by PC3 mock control cells in comparison to the PC3 ETS-1 blocked cells after 55 h (29).

either an ETS-1 inverse antisense expression vector or a mock control vector, and confirmed the blockade of ETS-1 using Western blot analysis (Fig. 4) (29).

We found that blockade of *ETS-1* in prostate cancer cells leads to a decrease in cell migration, suggesting a direct role of ETS-1 in this biological property (Fig. 5). However, blockade of ETS-1 did not have a significant effect upon the invasion of the cells (29). These findings indicate that ETS-1 reveals specificity for migration, but not invasion in the prostate cancer PC3 cell line examined (29).

In a follow-up study, we have investigated the effect of blocking ETS-1 in PC3 prostate cancer cells to the expression of genes known to be involved in various steps of the so-called metastatic cascade (such as proliferation, apoptosis, migration and angiogenesis) by a comprehensive gene expression microarray analysis of ETS-1 blocked cells compared to control cells (50).

Our study revealed many differentially expressed genes, however, only the genes with known roles in the metastatic cascade, and an expression of more than 10-fold increase or decrease between the ETS-1 blocked cells and the control were considered significant (50). Correlating these genes with genes found in a microarray analysis of prostate cancer tissues resulted in the identification of 16 genes that are either up- or down-regulated in prostate cancer tissues (Tables I and II) (50). Based on previous studies, 4 out of the 16 genes (*CD40, IGFBP3, FES* and *TLR4*) have already been reported to be regulated by members of the ETS family (reviewed in ref. 50). A follow-up bioinformatic analysis of these genes revealed that 13/16 of these genes have potential ETS-1 binding sites within their promoters (unpublished data).

As little is known about immune defenses in prostate cancer combined with the fact that the ETS family of transcription factors has been reported to be essential for the regulation of immunity-related genes (reviewed in ref. 51), we recently reported the identification of 37 immunity-related genes in prostate cancer tissues (52). Bioinformatic analysis revealed that 31 of these genes have potential binding sites within their promoter regions for members of the ETS family of transcription factors (52), and a few are known to be targets of ETS members (reviewed in ref. 52).

Table I. Genes that were found to be up-regulated in human prostate carcinomas compared to healthy glands of the prostate proper.

Gene	Full name
PRRX2	Paired related homeobox 2
ISL1	ISL LIM homeobox 1
NLRP2	NLR family, pyrin domain containing 2
BST2	Bone marrow stromal cell antigen 2
FOXL2	Forkhead box L2
EGR4	Early growth response 4

Candidate genes with a fold change of >2 and a P<0.01 are shown (50).

Table II. Genes that were found to be down-regulated in human prostate carcinomas compared to healthy glands of the prostate proper.

Gene	Full name
VAV3	Vav 3 guanine nucleotide exchange factor
FES	Feline sarcoma oncogene
PYCARD	PYD and CARD domain containing
TLR4	Toll-like receptor 4
IGFBP3	Insulin-like growth factor binding protein 3
CD40	CD40 molecule, TNF receptor superfamily member 5
GAS2	Growth arrest-specific 2; Fanconi anemia, complementation group F
SNCA	Synuclein, α (non-A4 component of amyloid precursor)
AMOT	Angiomotin
NPY1R	Neuropeptide Y receptor Y1

Candidate genes with a fold change of >2 and a P<0.01 are shown (50).

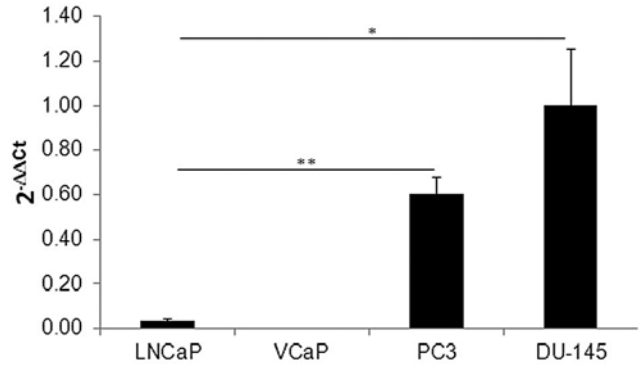

Figure 6. Expression of *ETS-1* in prostate cancer cell lines. The relative expression of *ETS-1* as measured by qRT-PCR among the DU-145, PC3, VCaP and LNCaP prostate cancer cell lines. Significance was calculated with the Student's t-test. $^{**}P<0.01$ and $^{*}P<0.05$ (45).

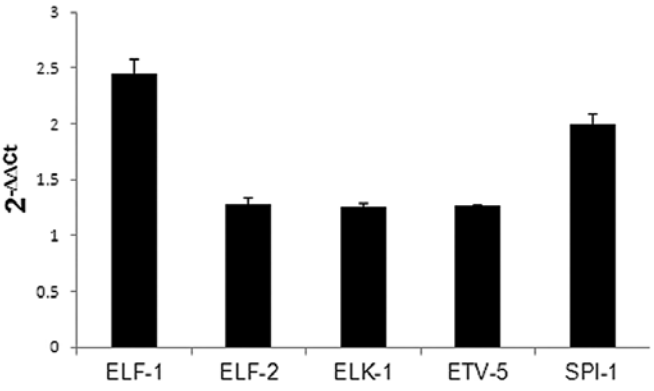

Figure 7. ETS-1 regulates other ETS family members in PC3 prostate cancer cell lines. QRT-PCR analysis using RNA extracted from ETS-1 blocked and mock control PC3 cells shows an up-regulation of the *ETS* family members *ELF-1, ELF-2, ELK-1, ETV-5* and *SPI-1* in *ETS-1* blocked cells compared to mock control (45).

In a follow-up study, we investigated in PC3 prostate cancer cells whether ETS-1 regulates some of these genes (53). We found 6 genes to be down-regulated (*BCL11A, CRISP3, DMBT1, FGR, NOS2* and *SAA1*) and 2 genes to be up-regulated (*CD38* and *HDAC9*) in PC3 cells with ETS-1 blockade compared to control cells (53). Our study provided evidence of the involvement of ETS-1 in the activation or repression of immunity-related genes and a potential key role that ETS-1 may play in prostate cancer immunology (53).

5. ETS-1, a potential regulator of the ETS-family in prostate cancer

As mentioned previously, the ETS family of transcription factors which has 27 known members in humans, is characterized by a highly conserved DNA-binding domain, the ETS domain, which consists of about 80 amino acids with 4 tryptophan repeats that recognizes DNA sequences containing a GGAA/T core motif (reviewed in refs. 5,19). Despite of the fact that the DNA-binding properties of the ETS members are similar, the different members may have preferences for distinct flanking sequences in the regulatory regions of genes, which may facilitate their binding specificity and subsequently their various functions (20). Furthermore, ETS members can also have overlapping functions, as well as redundant occupancy at proximal regulatory regions of genes (20,21). Therefore, it is plausible that different ETS members may compete for binding to the same ETS-binding sites (EBS) in the regulatory regions of target genes with different affinities (45), and that the trans-activation or trans-repression of genes could be a consequence of dynamic binding equilibrium as well as ternary complex formation of different ETS members and other transcription factors (22). It is conceivable that such a complex regulatory network involving different ETS members as well as ETS fusions could play a role in prostate cancer development and progression (45). Therefore, in a first step to unravel such a complex regulatory network, we have recently investigated whether ETS-1, the prototype of the family, regulates other family members in prostate cancer cell lines (45). We compared the expression level of *ETS-1*, among the androgen-insensitive DU-145 and PC3 cell lines, as well as the androgen-sensitive LNCaP and VCaP cell lines (45). We found *ETS-1* to be highly expressed in DU-145 and PC3 cell lines compared to LNCaP and VCaP cell lines (Fig. 6) (45).

As we have previously reported that ETS-1 has an effect upon the biological properties (29) and genes involved in the metastatic cascade in PC3 prostate cancer cells (50), combined with the findings that *ETS-1* is highly expressed in PC3 cells (45) (Fig. 6), we investigated the effect of ETS-1 blockade on the expression of the other ETS family members in this cell line (45).

Our study revealed that *ETS-1* selectively regulates the family members *ELF-1, ELF-2, ELK-1, ETV-5* and *SPI-1* in PC3 cells (Fig. 7) (45). Such findings indicate that ETS-1, the prototype of the family, is a potential 'master' regulator of other ETS family members, which could have significant implications in unraveling a complex network of different ETS factors in prostate cancer.

6. Conclusion

In prostate cancer, recurrent gene fusions involving members of the ETS family of transcription factors are frequently reported. Studies investigating the role of the ETS family prototype, ETS-1 in prostate cancer provide *in vitro* and *in vivo* evidence for the importance of ETS-1 in the development and progression of the disease. Evidence also implicates ETS-1 in prostate cancer immunology, and suggests that ETS-1 may potentially be a master regulator of other ETS family members. These findings do not only underline the importance of ETS-1 in prostate cancer, but also promote the idea that ETS-1 may become a suitable target of novel therapies in the future.

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