Am J Cancer Res 2020;10(10):3083-3105
www.ajcr.us /ISSN:2156-6976/ajcr0118419

Review Article

Function and regulation of the PEA3 subfamily of ETS transcription factors in cancer

Tingting Qi[1,2*], Qiang Qu[3*], Guohua Li[1,2], Jiaojiao Wang[1,2], Haihong Zhu[1,2], Zhi Yang[4], Yuesheng Sun[5], Qiong Lu[1,2], Jian Qu[1,2]

[1]Department of Pharmacy, The Second Xiangya Hospital, Central South University, Changsha 410011, PR China; [2]Institute of Clinical Pharmacy, Central South University, Changsha 410011, PR China; Departments of [3]Pharmacy, [4]General Surgery, Xiangya Hospital, Central South University, Changsha 410007, PR China; [5]Department of General Surgery, The Third Clinical College of Wenzhou Medical University, Wenzhou People's Hospital, Wenzhou 325000, PR China. [*]Equal contributors.

Received July 18, 2020; Accepted September 17, 2020; Epub October 1, 2020; Published October 15, 2020

Abstract: The PEA3 subfamily is a subgroup of the E26 transformation-specific (ETS) family. Its members, ETV1, ETV4, and ETV5, have been found to be overexpressed in multiple cancers. The deregulation of ETV1, ETV4, and ETV5 induces cell growth, invasion, and migration in various tumor cells, leading to tumor progression, metastasis, and drug resistance. Therefore, exploring drugs or therapeutic targets that target the PEA3 subfamily may contribute to the clinical treatment of tumor patients. In this review, we introduce the structures and functions of the PEA3 subfamily members, systematically review their main roles in various tumor cells, analyze their prognostic and diagnostic value, and, finally, introduce several molecular targets and therapeutic drugs targeting ETV1, ETV4, and ETV5. We conclude that targeting a series of upstream regulators and downstream target genes of the PEA3 subfamily may be an effective strategy for the treatment of ETV1/ETV4/ETV5-overexpressing tumors.

Keywords: PEA3 subfamily, transcription factor, cancer, metastasis, resistance

Introduction

The E26 transformation-specific (ETS) family is one of the largest families of signal-dependent transcription factors, consisting of 28 protein-coding genes in the human genome [1, 2]. A common feature of these ETS transcription factors is that they share an identical DNA binding domain (the ETS domain) that can bind to the core DNA sequence 5'-GGA(A/T)-3' [3]. According to previous reports, ETS transcription factors participate in tumorigenesis and developmental processes by regulating a variety of biological processes, including cell proliferation, migration, apoptosis, senescence, angiogenesis, and stem cell development [4].

Based on their similarities, including high amino acid conservation in the ETS-domains and subgroup-specific amino acid sequences, ETS transcription factors have been classified into several different subfamilies [5]. The ERG and PEA3 subfamilies have received particular research attention owing to their important roles in cancer progression and metastasis. The ERG subfamily comprises ERG, FLI1, and FEV, which are generally overexpressed in prostate cancer and Ewing's sarcoma owing to gene fusions. The PEA3 subfamily not only participates in tumorigenesis and tumor progression in prostate cancer and Ewing sarcoma, it also has complex and diverse roles in multiple types of tumors.

The PEA3 subfamily contains three transcription factors: PEA3/E1AF/ETV4, ER81/ETV1, and ERM/ETV5. Overexpression of ETV1, ETV4, and ETV5 is found in many tumors. High levels of these transcription factors usually lead to a more aggressive tumor phenotype and drug resistance [6]. ETV1 is often deregulated in prostate cancer [7, 8] and has been shown to be specifically expressed in the majority of gastrointestinal stromal tumors (GISTs) [9]. The

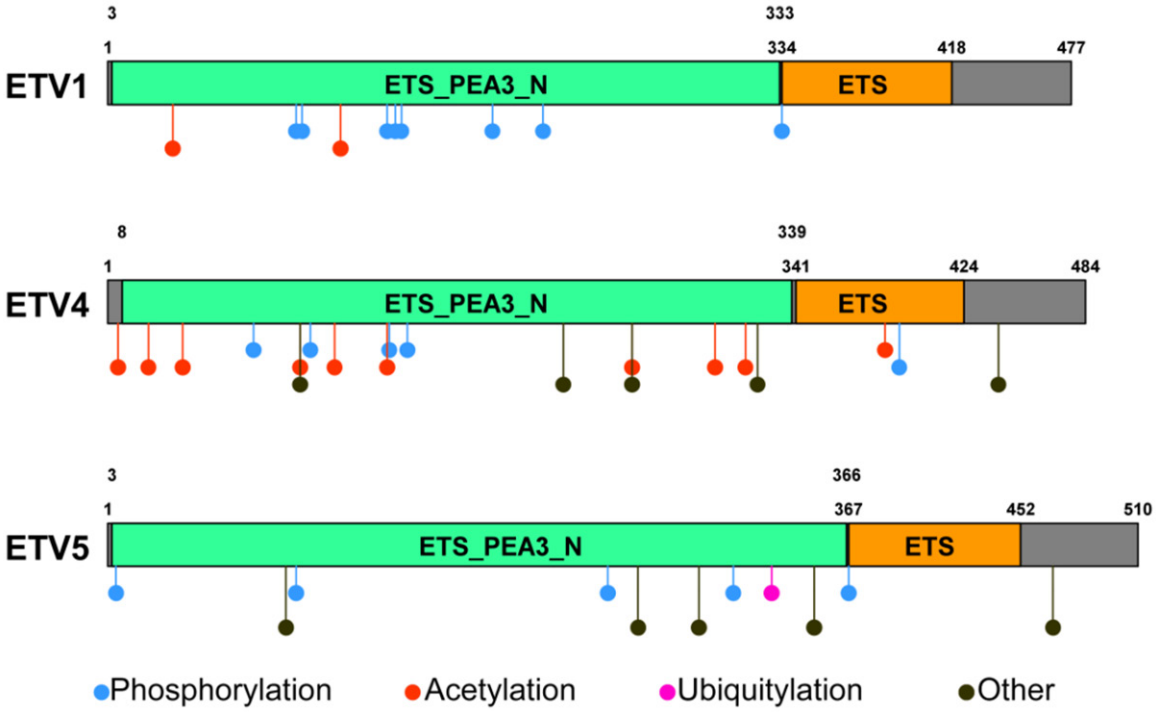

Figure 1. Conserved domains of the PEA3 subfamily. ETV1, ETV4, and ETV5 share an ETS domain and PEA3-type ETS transcription factor N-terminal domain. Post-translational modifications identified as phosphorylation sites, acetylation sites, and ubiquitination sites are highlighted.

ETV4 transcription factor is frequently activated in gastric cancer [10], lung cancer [11], hepatocellular carcinoma (HCC) [12], and colorectal cancer (CRC) [13]. ETV5 is correlated with fertility and has been implicated in the progression of endometrial cancer [14] and ovarian cancer [15]. Owing to the extensive carcinogenesis associated with the PEA3 subfamily, ETV1, ETV4, and ETV5 have been proposed as prognostic markers in tumor patients.

However, oncogenic transcription factors are considered "undruggable" by conventional methods, hence it is necessary to better understand the protein structures, precise functions, and specific mechanisms of the PEA3 subfamily in cancer. Here, we review the genes and pathways upstream and downstream of the PEA3 subfamily. As oncogenic transcription factors, ETV1, ETV4, and ETV5 induce cancer progression by regulating multiple biological processes, including epithelial-mesenchymal transition (EMT), the cell cycle, apoptosis, cell migration, the maintenance of cancer stem cell (CSC) phenotype, and chemotherapy resistance. Therefore, targeting PEA3-related genes and pathways, or directly targeting the PEA3 subfamily, may improve cancer treatment and, more importantly, may provide options to overcome drug resistance.

Structures and functions of the PEA3 subfamily

ETV1, *ETV4*, and *ETV5* are protein-coding genes with DNA-binding transcription factor activity. In humans, *ETV1* is located on chromosome 7q22, whereas *ETV4* and *ETV5* are located on 17q21 and 3q27, respectively. The protein structures of ETV1, ETV4, and ETV5 are more than 95% identical within the DNA-binding domain [16]. All three transcription factors share two conserved domains: the ETS domain and the PEA3-type ETS transcription factor N-terminal domain (**Figure 1**). The N terminus of the PEA3 transcription factors is involved in transactivation and inhibition of DNA binding [16]. The N terminus contains conserved mitogen-activated protein kinase (MAPK) phosphorylation sites, and transactivation is enhanced by the MAPK signaling pathway [17]. Both N- and C-terminal inhibitory domains that repress DNA binding were identified and shown to mediate autoinhibition of DNA binding [18]. Post-

translational modifications of ETV1 and *E*TV4 include phosphorylation and acetylation, whereas ETV5 contains post-translational phosphorylation and ubiquitination sites (**Figure 1**).

Functionally, the PEA3 subfamily is correlated with motor coordination, axon guidance, neuron development, metabolism, hormonal regulation, fertility, and tumorigenesis. As the expression levels of ETV1, ETV4, and ETV5 may be different in specific tissues and organs, their functional tendencies may also differ.

ETV1 has been reported to be an important regulator in cardiac disease. For example, ETV1 expression is enriched in fast conduction tissues and was shown to be essential for rapid conduction in the heart, whereas ETV1 deficiency resulted in cardiac conduction defects and hypoplasia of the ventricular conduction system [19]. Besides, it was reported recently that ETV1 is upregulated in atrial biopsies from patients with atrial fibrillation and is responsible for arrhythmia; this highlights its regulatory role in atrial remodeling [20, 21]. ETV1 is important for muscle organ development. For instance, ETV1 controls the innervation of facial muscles; therefore, its loss may induce facial synkinesis in humans [22]. ETV1 is also crucial for the development of the cerebellar circuit, functioning as a transcriptional determinant of the terminal program of cerebellar development by upregulating maturation genes and downregulating immaturation genes [23, 24]. As a downstream gene of fibroblast growth factor signaling, ETV1 also has a role in coordinating the development of the Xenopus forebrain [25]. In addition, as a differentiation-related transcription factor, ETV1 is a critical gene in cementogenesis and periodontal ligament cell differentiation [26].

ETV4 and ETV5 are positively regulated by brain-derived neurotrophic factor (BDNF) in hippocampal neurons and are essential for hippocampal dendrite/synapse development [27]. Besides, overexpression of ETV4 and ETV5 was shown to promote BDNF-induced neurite outgrowth in dorsal root ganglion neurons [28]. These results indicate that ETV4 and ETV5 have key roles in normal neural axonal growth and development [29]. According to previous studies, ETV4 and ETV5 are downstream genes of RET (RET mutation usually leads to renal agenesis); therefore, they are both required for kidney development [30]. Mechanistically, ETV4 and ETV5 promote normal kidney development by mediating the formation of the ureteric bud tip domain and inducing directed cell movements in the ureteric bud tips [31, 32].

It is well known that ETV4 and ETV5 are closely related to fertility in both males and females. Mechanistically, ETV5 is upregulated by sex-determining gene *SRY-box9* (*SOX9*) and is essential for spermatogonial stem cell self-renewal. Therefore, ETV5 is indispensable for normal spermatogenesis [33, 34]. ETV4 and ETV5 also have important roles in ovarian function. Jinwon et al. found that ETV4 and ETV5 were expressed in granulosa and cumulus; further studies indicated that they promote oocyte maturation and ovulation by upregulating cyclooxygenase-2 (PTGS2), a rate-limiting enzyme for prostaglandin synthesis [35]. As a target gene of Src family kinase, *ETV5* was also found to promote self-renewal of female germline stem cells [36]. Besides, *ETV5* mutation can lead to developmental abnormalities in mice, including postnatal growth restriction, renal asymmetry, and polydactyly [37]. *ETV5* is also thought to be an obesity-related gene that is crucial for the regulation of energy balance and metabolism, for example, by regulating insulin secretion and circulating glucocorticoids [38, 39].

In summary, the PEA3 subfamily is important for fertility, development, and metabolic processes. In addition, the PEA3 subfamily is actively involved in tumorigenesis, especially tumor metastasis. The present study focused on the role of the PEA3 subfamily in tumor progression, metastasis, and resistance.

Molecular mechanisms of PEA3 subfamily activation

The PEA3 subfamily can be activated by many factors. The RAS-RAF-MEK-ERK (MAPK) signaling pathway is its best known upstream positive regulator. *Capicua* (*CIC*) is a tumor suppressor downstream of the MAPK pathway. The loss of *CIC* usually increases the expression of PEA3 subfamily members by directly binding to their promoter regions. Some microRNAs (miRNAs) have been shown to inhibit PEA3 expression at the post-transcriptional level; alterations to these miRNAs usually lead to PEA3 subfamily dysregulation. Gene fusions of *EWS/PEA3* and

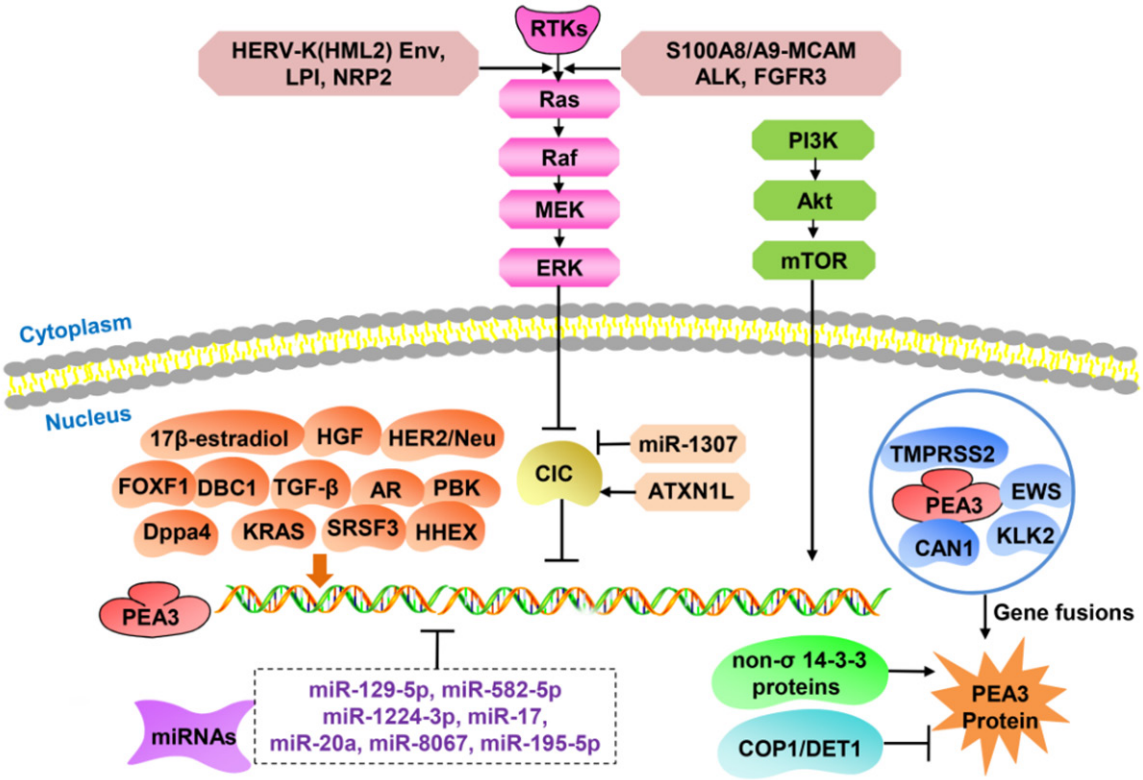

Figure 2. Multiple genes and signaling pathways regulate expression of the PEA3 subfamily. The PEA3 subfamily can be activated by a series of genes and pathways: activation of the MAPK and PI3K/Akt signaling pathways, loss of PEA3 repressors (*CIC*, *COP1*, and *DET1*), gene fusions, and miRNA-mediated post-transcriptional regulation.

TMPRSS2/PEA3 are well known to increase ETV1/ETV4/ETV5 protein levels, subsequently inducing cell migration and invasion. Besides, several studies have reported that PI3K/Akt signaling could activate *ETV1/ETV4/ETV5* expression. The molecular mechanisms of *ETV1/ETV4/ETV5* activation are shown in **Figure 2**.

Activation of the RAS-RAF-MEK-ERK pathway

The MAPK signaling pathway is often abnormally activated in tumors; therefore, many researchers have suggested targeting RAS-RAF-MEK-ERK signaling for cancer therapy [40]. Many factors can induce MAPK signaling activation; these include members of the receptor tyrosine kinase (RTK) family [41]. Here, we found that four RTKs (KIT, PDGFRA, Met, and EGFR) could upregulate the expression of the PEA3 subfamily by activating the MAPK signaling pathway.

GISTs are characterized and defined by an activating mutation of KIT or PDGFRA [42-44]. It has been reported that KIT and PDGFRA could synergistically activate the MAPK pathway and lead to significant overexpression of *ETV1*, a master regulator of GIST-specific transcription network [42], eventually causing liver metastasis of GIST [45]. *ETV1* can in turn directly bind to the promoter region of KIT; therefore, KIT and *ETV1* form a positive feedback circuit that promotes GIST development [44]. Crenolanib besylate, an inhibitor of PDGFRA, was found to partially reduce *ETV1* expression by disrupting the MAPK pathway, thereby providing a therapeutic strategy for KIT-mutant GIST [46]. KIT has also been found to promote the expression of *ETV4* by phosphorylating ERK and inducing migration of colorectal mucinous adenocarcinoma [47].

In gastric cancer and lung cancer, Met overexpression was shown to activate the RAS-RAF-MEK-ERK pathway; this subsequently increased *ETV1/ETV4/ETV5* expression and eventually promoted cell migration and invasion by regulating matrix metalloproteinase 2 (*MMP2*) expression [48].

Bunda et al. recently identified a mechanism by which EGFR could increase the expression of *ETV5* in two parallel ways [49]. On the one hand, EGFR activation led to ERK-mediated serine-phosphorylation, which reduced the levels of *CIC*, thereby disrupting the DNA combination of *ETV5* and *CIC* [50]. On the other hand, EGFR activated c-Src kinase, resulting in tyrosine-phosphorylation of free *CIC* and promoting its nuclear export [49]. Therefore, combined inhibition of ERK and c-Src may be useful for the reduction of *ETV5* expression in glioblastoma (GBM).

In addition to these RTKs, some other factors can activate the RAS-RAF-MEK-ERK signaling pathway. For instance, binding of melanoma cell adhesion molecule (*MCAM*) to an extracellular cytokine S100A8/A9 can accelerate the aggressiveness of breast cancer and melanoma. Mechanistically, S100A8/A9-*MCAM* binding activates ERK1/2 and mitogen-activated protein kinase kinase kinase 8 (MAP3K8), which further triggers downstream *ETV4* expression, leading to tumor metastasis [50, 51]. A human endogenous retrovirus-derived gene *HERV-K (HML2) Env* was also shown to activate the ERK1/2 pathway and increase the expression of *ETV4* and *ETV5*, which contributed to breast oncogenesis [52]. Lysophosphatidylinositol increased ERK phosphorylation through coupling with $G_{q/11}$ and activating orphan receptor GPR55, which further activated *ETV4* expression, thus driving malignant growth and metastasis of triple-negative breast cancer [53].

Anaplastic lymphoma kinase (ALK)-activating mutations upregulate *ETV5* expression through the RAS/MAPK axis in neuroblastoma [54]. Activating mutations of fibroblast growth factor receptor 3 (*FGFR3*) induce a high level of *ETV5* mediated by MAPK/ERK in bladder cancer [55]. Similarly, transmembrane and soluble neuropilin-2 (NRP2) was shown to induce *ETV4* expression through the NRP2-ERK-MAPK-ETV4 axis in oesophageal squamous cell carcinoma [56].

Consequently, these RTKs and cytokines increase ERK phosphorylation and lead to the activation of MAPK signaling pathway. As an upstream regulator of *ETV1/ETV4/ETV5*, the MAPK pathway causes overexpression of *ETV1/ETV4/ETV5* in different types of tumors.

Loss of ETV1/ETV4/ETV5 repressors

CIC is an acknowledged tumor suppressor and transcriptional repressor that is negatively regulated by RAS/MAPK signaling [57, 58]. *ETV1*, *ETV4*, and *ETV5* are the best known downstream targets of *CIC*. Thus, *CIC* loss usually induces overexpression of *ETV1/ETV4/ETV5* [6, 59].

Zhou et al. confirmed that *CIC* was negatively regulated by *miR-1307*, and identified a direct binding motif between *miR-1307* and the 3' untranslated region (3'-UTR) of *CIC*. This *miR-1307/CIC* axis further causes accumulation of *ETV4* and *ETV5* in ovarian cancer [60]. Likewise, *ETV4* and *ETV5* have been shown to be overexpressed in breast cancer [61] and multiple myeloma [62], whereas *ETV1*, *ETV4*, and *ETV5* were all derepressed in pancreatic cancer owing to the loss of *CIC* [6].

Research in CRC showed that *CIC* expression was decreased in CRC tissues compared with paired normal tissues. Besides, a negative correlation was found between *CIC* and the PEA3 subfamily. *ETV4* was the most upregulated transcription factor in the PEA3 subfamily in CRC [59]; similarly, *ETV4* was the most significantly overexpressed member of the PEA3 subfamily in *CIC*-deficient HCC [63]. The inactivation of *CIC* in lung cancer also led to the derepression of *ETV4* [64]. These outcomes suggest that *ETV4* may play a more important role in CRC, HCC, and lung cancer.

Similar to *CIC*, E3 ubiquitin ligase constitutive photomorphogenetic 1 (COP1) protein is a repressor of the PEA3 subfamily [65]. Mechanistically, COP1 binds to the two motifs in conserved VP residues in the N terminus of PEA3 subfamily and leads to the ubiquitination degradation of *ETV1/ETV4/ETV5* [65, 66]. Therefore, the loss of COP1 blocks the binding of COP1 to *ETV1/ETV4/ETV5*, thereby enhancing the expression levels of *ETV1/ETV4/ETV5*.

In GIST and melanoma, COP1 and DET1 deficiency were shown to lead to the maintenance of ETV1 protein levels [67]. Overexpression of *ETV1* induced by COP1 deficiency has also been reported in other tumor types, including renal cell carcinoma (RCC) [68], breast cancer [69], and prostate cancer [65]. As well as *ETV1*, *ETV4* was also correlated with COP1 loss in

GIST. As expected, a reduction in COP1 levels resulted in *ETV4* accumulation [70].

Post-transcriptional regulation mediated by miRNAs

miRNAs are well known to mediate gene inhibition by binding to the 3'-UTRs of their target genes. Here, we found several miRNAs targeting *ETV1* and *ETV5*. Gao et al. confirmed that *ETV1* was a direct target of *miR-129-5p*, and that *ETV1* was negatively regulated by *miR-129-5p* in prostate cancer [71]. This indicates that *miR-129-5p* could serve as a therapeutic target to inhibit prostate cancer progression and metastasis by decreasing the transcriptional activity of *ETV1*. A recent study found that the *circ-ZNF609/miR-1224-3p/ETV1* axis was involved in lung adenocarcinoma (LAUD) progression: *circ-ZNF609* acted as a sponge for *miR-1224-3p* to reduce *miR-1224-3p* expression, which subsequently increased *ETV1* expression and finally led to LAUD progression [72]. Similarly, the *circRNA_001160/miR-195-5p/ETV1* axis was identified as a potential therapeutic target to increase blood-tumor barrier permeability in glioma [73]. Besides, *miR-582-5p* was found to be a negative regulator of *ETV1* in lung cancer [74]. In triple-negative breast cancer, *miR-17-5p* was found to inhibit cell proliferation and invasion by directly targeting *ETV1* [75]. In GIST, *miR-17* and *miR-20a* were found to reduce cell proliferation and accelerate cell apoptosis by inhibiting *ETV1* transcription [76]. On the contrary, Cohen et al. found that *miR-17* functioned as an oncogenic miRNA in melanoma; *miR-17* promoted cell motility and cancer metastasis by inhibiting *ETV1* expression, indicating that *ETV1* could inhibit cell migration and motility in melanoma cells [77]. In contrast to *ETV1*, miRNAs targeting *ETV4* and *ETV5* have been rarely reported. Wang et al. found that *ETV5* was negatively regulated by *miR-8067* in GBM and recommended *miR-8067* as a candidate therapeutic target for GBM [78].

In summary, the PEA3 subfamily is negatively regulated by several miRNAs. The dysregulation of miRNAs may alter the expression levels of *ETV1*, *ETV4*, and *ETV5*, leading to cancer progression and metastasis. Furthermore, these miRNAs could serve as therapeutic targets by regulating *ETV1/ETV4/ETV5* expression in cancer treatment.

Gene fusions induced by chromosome rearrangement

Chromosome rearrangements related to the ETS family occur in 50-70% of prostate cancer cases [79], and represent the main cause of this cancer [2]. Such chromosome rearrangements occur when androgen-regulated gene promoters are fused to the ETS genes, leading to high levels of ETS oncoproteins [80]. Transmembrane serine protease 2 (*TMPRSS2*) is an androgen-regulated prostate-specific gene that is involved in the vast majority of gene fusions in prostate cancer [81]. Compared with fusion-negative patients, expression levels of PEA3 subfamily members were found to be elevated hundreds of folds in the fusion-positive patients [82].

Among the gene fusions between *TMPRSS2* and the ETS family, the *TMPRSS2-ERG* fusion is the most frequent, occurring in approximately 50% of cases, followed by *TMPRSS2-ETV1* (10%), *TMPRSS2-ETV4* (< 1%), *TMPRSS2-ETV5* (< 1%), and *TMPRSS2-FLI1* (< 1%) [1, 83-85]. Although the frequency of *ETV1*, *ETV4*, and *ETV5* gene fusions are not as high as those of *ERG*, they are thought to be among the major driving forces of higher-grade tumors owing to the invasive potential they confer [86]. In support of this, Dedigama-Arachchige et al. observed that *ETV4* expression was mainly expressed in high-grade prostate cancers [87]. Additional 5' fusion partners of *ETV1/ETV4/ETV5* have been reported; these gene fusions include *SNRPN-ETV1*, *MALAT1-ETV1*, *OR51E2-ETV1*, *KLK2-DGKB-ETV1*, *UBTF-ETV4*, *SLC45-A3-ETV4*, *HERVK17-ETV4*, and *EWS-ETV1/ETV4/ETV5* [85, 88, 89]. All of these gene fusions cause enrichment of *ETV1/ETV4/ETV5*, which contributes to the progression and metastasis of prostate cancer.

Compared with prostate cancer, chromosome rearrangement occurs more frequently in Ewing's sarcoma (approximately 85% of cases) [90]. In contrast to the *TMPRSS2-ETS* gene fusions in prostate cancer, *EWS* is the most common fusion partner of the ETS family in Ewing's sarcoma [91, 92], with *EWS-FLI1* accounting for 90% of all gene fusions, followed by *ERG* (5%), *ETV1* (1%), *ETV4* (1%), and *FEV* (1%) [93]. These *EWS/ETS* gene fusions can activate human telomerase activity through upregulating *TERT* (a target of *EWS/ETS*), caus-

ing the development of Ewing's sarcoma and increasing its invasiveness [94].

Recently, a novel gene fusion, *PTPRZ1-ETV1*, was detected in gliomas. This may provide a new therapeutic target, given the carcinogenic potential of *PTPRZ1* and *ETV1* in other tumors [95].

Effects of PI3K/Akt signaling and other factors

In addition to the MAPK signaling pathway, PI3K/Akt signaling was reported to induce the overexpression of the members of PEA3 subfamily. In clear cell RCC, PI3K/Akt signaling activates *ETV4* expression, then *ETV4* promotes cell migration by directly binding to its downstream promoter *FOSL1* [96]. In advanced prostate cancer, *ETV4* (rather than *ETV1* or *ETV5*) is overexpressed under the combinatorial activation of the PI3-kinase and RAS signaling pathways, indicating that *ETV4* may represent an effective therapeutic target in metastatic prostate cancer [97].

Many other factors can activate PEA3 subfamily overexpression. In GIST, *FOXF1* directly regulates the expression of *ETV1* by binding to the *ETV1* enhancer sites [98]. In GBM, ETV1-E7 inclusion can be induced by serine and arginine rich splicing factor 3 (SRSF3), a splicing factor responsible for tumorigenesis and tumor progression, resulting in increased stability of the ETV1 protein [99].

The *KRAS* oncogene has been reported to induce *ETV4* expression, which suppressed *PDCD4* expression and improved the invasiveness of pancreatic ductal adenocarcinoma cells [100]. The *ETV4* transcription factor was also upregulated by stimulation with hepatocyte growth factor (HGF), a scatter factor involved in cell invasion [101], contributing to the malignancy potential of non-small-cell lung cancer (NSCLC) [102, 103] and oral squamous cell carcinoma (OSCC) [104]. Depletion of acetyl-CoA carboxylase (ACC1) and ATP citrate lyase (ACLY) upregulated *ETV4* levels through reduction of α-ketoglutarate, which further protected lung cancer cells from hypoxia-induced apoptosis [105]. PDZ-binding kinase (PBK) was found to induce HCC metastasis by enhancing the binding of *ETV4* to its promoter *uPAR* [12]. In addition, *ETV4* gene expression was significantly enhanced by 17β-estradiol, a potent estrogenic agent, inducing proliferation and invasiveness of cholangiocarcinoma [106]. In 3T3 fibroblasts, developmental pluripotency associated factor 4 (*Dppa4*) activated *ETV4* expression and induced a tumor phenotype [107].

In additional sex combs-like 1 (*ASXL1*)-mutated myeloid leukemia, Hematopoietically Expressed Homeobox (*HHEX*) promoted myeloid leukemogenesis by directly upregulating *ETV5* expression, indicating that *ETV5* may be a critical target for *ASXL1*-mutated myeloid malignancies [108].

In prostate cancer, non-σ 14-3-3 proteins were also found to increase ETV1 protein levels by binding to ETV1 and protecting it from degradation [109]. Besides, androgen-activated androgen receptor could increase expression of *ETV1*, directly activating the *Twist1* promoter to induce EMT and tumor metastasis [110].

In breast cancer, transforming growth factor β (*TGF*-β) could recruit *ETV4* to open chromatin regions and induce EMT [111]. Deleted in breast cancer 1 (*DBC1*) acted as a coactivator of *ETV4* to drive the progression of estrogen receptor-negative breast cancer [112]. In addition, *ETV1* transcription factor could be activated by proto-oncoprotein *HER2/Neu* in breast cancer, endometrial cancer, and ovarian cancer, thereby promoting tumorigenesis and metastasis [113, 114].

Various functions of the PEA3 subfamily in cancer

The most common function of the PEA3 subfamily is to promote cell migration and invasion, thereby contributing to tumor progression and metastasis. Here, we summarize the involvement of the PEA3 subfamily in multiple processes associated with tumor progression and metastasis. As shown in **Figure 3**, the PEA3 subfamily members regulate many genes related to EMT, the cell cycle, apoptosis, cell migration and invasion, the CSC phenotype, and chemotherapy resistance. Therefore, targeting the PEA3 subfamily and its downstream genes could provide effective treatments for cancer.

PEA3 subfamily induces EMT

EMT is the transformation of epithelial cells to mesenchymal cells, which reduces their adhe-

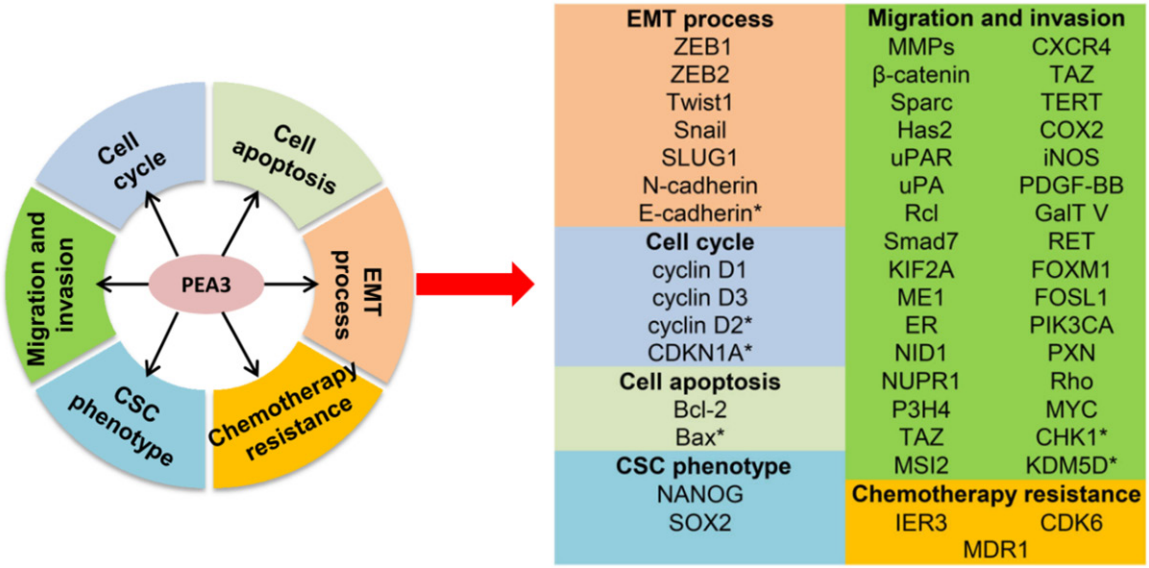

Figure 3. Roles of the PEA3 subfamily in cancer. The PEA3 subfamily influences cancer progression and metastasis by regulating the cell cycle, apoptosis, EMT, cell migration and invasion, development of the cancer stem cell phenotype, and chemotherapy resistance. *Genes downregulated by PEA3 subfamily.

sion ability and enhances their mobility. Multiple studies have shown that EMT plays an important part in promoting migration and invasion of tumor cells [115-117]. The PEA3 subfamily can enhance the EMT process by directly or indirectly regulating EMT markers including *ZEB1*, *ZEB2*, *Twist1*, *Snail*, *N-cadherin*, and *SLUG1*.

In breast cancer, *ETV4* was shown to activate the expression of *ZEB1* and *Snail* by directly binding to the promoter regions of *ZEB1* and *Snail*, leading to EMT and promoting metastasis [51, 118]. In prostate cancer, *ETV1* and *ETV4* significantly increased the expression of several mesenchymal markers, including *Twist1*, *SLUG1*, *ZEB1*, *ZEB2*, and *N-cadherin* [110, 119]. Similar results were found in CRC, where *ETV4* enhanced the expression of EMT markers [13]. Besides, epithelial marker *E-cadherin* was reduced in oesophageal squamous cell carcinoma in response to *ETV4* overexpression [56]. In gastric cancer, EMT and metastasis could be partly attributed to the overexpression of *Snail* induced by *ETV1* [120].

The *ETV5* transcription factor was shown to be closely related to papillary thyroid cancer cell growth by directly targeting *Twist1* to trigger the EMT process [121]. In endometrial cancer, *ETV5* promoted the invasive potential of tumor cells by upregulating *ZEB1* and downregulating *E-cadherin* [122].

PEA3 subfamily promotes cell migration and invasion

It is well acknowledged that *ETV1*, *ETV4*, and *ETV5* are involved in tumor progression and metastasis, but how they regulate cell migration and invasion has not been systematically reported. Here, we summarize some genes related to cell migration and invasion regulated by the PEA3 subfamily in multiple cancers.

In prostate cancer, *ETV1* is a negative regulator of checkpoint kinase 1 (CHK1). Inhibition of CHK1 by *ETV1* overexpression results in accumulation of DNA damage and promotes invasive tumorigenesis [123]. MMPs are common genes related to cell migration and invasion. *ETV1* can stabilize β-catenin and directly bind to *MMP1/7*, leading to increased accumulation of β-catenin and *MMP1/7*, and inducing migration and invasion of prostate cancer cells [7, 109, 124]. By binding to the promoter of *TAZ* [125] or *uPA* [126], *ETV4* can significantly increase *TAZ/uPA* expression, which contributes to tumor metastasis. As an oncogenic transcription factor, *ETV4* was also found to directly bind to the 5' and 3' *MYC* enhancers [127], indicating that *ETV4* may regulate the expression of some key oncogenes.

In bladder cancer, the PEA3 subfamily has been shown to be responsible for tumor invasion and metastasis by directly binding to the promoter region of *P3H4* [128] and *TAZ* [55]. In OSCC [104], oesophageal squamous cell carcinoma [56], and oesophageal adenocarcinoma [129], *ETV4* overexpression dramatically increased MMP levels and drove metastatic progression. Besides, the PEA3 subfamily can regulate many genes in other types of tumors; these are listed in Table S1.

According to these studies, the PEA3 subfamily regulates the expression of various genes related to tumor migration and invasion, implying that PEA3 subfamily members and their downstream genes could be effective therapeutic targets for metastatic tumors.

PEA3 subfamily regulates cell cycle and apoptosis

Studies have shown that *ETV1*, *ETV4*, and *ETV5* contribute to cell cycle progression [76, 119, 128, 130] and protect cells from apoptosis [10, 131]. Abnormal overexpression of cyclin D1 usually contributes to cell cycle progression and cyclin D1 expression has been found to be promoted by *ETV4* activation in pancreatic cancer [132, 133] and GIST [70]. As expected, *TMPRSS2-ETV5* gene fusion also led to high levels of cyclin D1 in prostate cancer [134]. p21 is a cyclin-dependent kinase inhibitor that plays an important part in cancer proliferation by regulating cell cycle progression [135]. Cos et al. found that *ETV4* could downregulate p21 protein levels through directly binding to the *CDKN1A* promoter and downregulating p53 protein in *ETV4* transgenic mouse model, resulting in the development of mouse prostatic intraepithelial neoplasia [136]. In breast cancer, *ETV4* promoted cell proliferation by negatively regulating its downstream target gene cyclin D2 [137] and positively regulating cyclin D3 [138].

In response to overexpression of *ETV1*, expression of anti-apoptotic protein Bcl-2 was increased and that of pro-apoptotic protein Bax was reduced in GIST, which prevented apoptosis of tumor cells [139]. Moreover, *ETV1* was overexpressed in breast cancer cells, whereas knockdown of *ETV1* significantly increased cell apoptosis rate and inhibited tumor growth in mice [130].

PEA3 subfamily maintains the cancer stem cell phenotype

CSCs represent an extremely small subset of cancer cells with unlimited self-renewal and differentiation potential, which results in the malignant proliferation of tumors [140]. CSCs have been reported to be responsible for the development of drug resistance, and for cancer metastasis and recurrence [141]. As mentioned, *CIC* is a negative regulator of the PEA3 subfamily and a known tumor suppressor. More importantly, *CIC* deficiency was found to induce CSC characteristics through the derepression of *ETV4/ETV5* in breast cancer [61] and oligodendroglioma [142].

NANOG and *SOX2* are stem cell transcription factors that contribute to the maintenance of embryonic cell pluripotency and cancer cell stemness [143, 144]. Park et al. found that *NANOG* was activated by the *ETV4* transcription factor in human embryonic carcinoma NCCIT cells through the ETV4-ETS binding site [145]. In addition, a positive correlation between *ETV4* and *SOX2* was found in squamous cell carcinomas [146], indicating that *ETV4* may play an important part in the maintenance of CSC characteristics.

PEA3 subfamily mediates chemotherapy resistance

Based on the results discussed above, the accumulation of the PEA3 subfamily is primarily due to MAPK pathway activation stimulated by RTKs. *CIC* is a downstream effector of MAPK, which is negatively regulated by the MAPK pathway. Interestingly, many studies have reported that *CIC* loss was closely related to drug resistance independent of the MAPK signaling pathway.

In BRAF-mutated multiple myeloma, a combination of dabrafenib and trametinib was shown to effectively block the RAS-BRAF-MEK-ERK pathway, but a subset of patients could develop drug resistance due to *CIC* mutation [62]. Mechanistically, mutation or downregulation of CIC increases the expression of its downstream target genes *ETV1*, *ETV4*, and *ETV5*, which subsequently confers MEK-BRAF inhibitor resistance. Similar mechanisms have been found in several other tumors. For example, *CIC* inactivation drove the development of resistance to

trametinib (MAPK inhibitor) in human T-cell lymphoblastic lymphoma [58] and pancreatic cancer [6] by restoring the expression of *ETV1*, *ETV4*, and *ETV5*, which are necessary for the full resistance mediated by *CIC* loss. Besides, the activation of *ETV1* contributed to resistance to gefitinib (an EGFR inhibitor) mediated by *CIC* deficiency in NSCLC [147]. *ETV5* was found to be a potential target to overcome resistance to cetuximab (a monoclonal antibody against EGFR) in CRC [148].

Zhou et al. found that *miR-1307* was involved in chemoresistance in ovarian cancer, and identified a direct binding motif between *miR-1307* and the 3'-UTR of *CIC*, indicating that *CIC* is a downstream target of *miR-1307* [60]. Therefore, targeting the *miR-1307-CIC-ETV1/ETV4/ETV5* axis may increase drug sensitivity.

In addition to *CIC* loss, *COP1* and *DET1* loss also resulted in E*TV1/ETV4/ETV5* overexpression. In GIST and melanoma, loss of *COP1* and *DET1* led to maintenance of ETV1 protein levels, and resistance to MAPK inhibitors (including imatinib, trametinib, and vemurafenib) eventually developed in vitro and in vivo [67].

Recent studies also found that *ETV4* and *ETV5* could act as biomarkers for drug response [149]. *ETV4* was correlated with clinical response to MEK inhibitors in melanoma; however, *ETV4* depletion did not alter sensitivity to selumetinib or trametinib [150]. Copy number alterations of *ETV5* in the 3q chromosomal arm are predictive biomarkers of immune checkpoint inhibitor response in advanced cutaneous squamous cell carcinoma [151]. PEA3 subfamily could also regulate the expression of genes related to drug resistance by binding to a variety of downstream targets. CHEN et al. showed that *ETV4* overexpression protected HCC cells from apoptosis and promoted resistance to sorafenib and cisplatin by directly binding to the promoter region of *IER3*, an oncogene related to tumor progression and drug resistance [131]. In melanoma, *CDK6* induced resistance to BRAF inhibitor vemurafenib by altering the cell cycle. Further analysis revealed that the JUN family and *ETV5* are key regulators of *CDK6* [152]. Therefore, *ETV5* is involved in resistance to BRAF inhibition in melanoma. Multi-drug resistance protein 1 (MDR1) is known to induce chemotherapy resistance in multiple cancers. In gastric cancer, ETV4 was found to activate MDR1 expression, which conferred chemotherapy resistance [153].

In summary, the loss of PEA3 repressors *CIC*, *COP1*, and *DET1* could maintain the expression of *ETV1/ETV4/ETV5* independently of the MAPK signaling pathway, leading to MAPK inhibitor resistance. In addition, *ETV1*, *ETV4*, and *ETV5* could regulate the expression of their downstream genes related to drug resistance, thereby also mediating drug resistance (**Table 1**). Combined targeting of the MAPK signaling and the PEA3 subfamily may increase the sensitivity of cancers to chemotherapy drugs.

Controversy regarding the PEA3 subfamily as carcinogenic transcription factors

HER2/Neu overexpression occurs frequently in breast cancer and usually leads to an aggressive tumor phenotype. As described above, *ETV1* contributes to tumorigenesis and metastasis in breast and ovarian cancers via *HER2/Neu* stimulation. Besides, the PEA3 subfamily promotes breast cancer cell migration and invasion by regulating the expression of its downstream genes, including *hTERT*, *Rcl*, *Smad13*, *CXCR4*, and MMPs. However, a few studies have reported that the PEA3 subfamily could inhibit breast cancer development and progression.

Hu et al. [154] and Xing et al. [155] found that *ETV4* suppressed tumor growth and invasiveness by directly binding to the *HER2/Neu* promoter in prostate cancer, breast cancer, and ovarian cancer. These two studies indicated that *HER2/Neu* was negatively regulated by *ETV4*, thereby providing a therapeutic strategy for *HER2/Neu*-overexpressing tumors. However, Span et al. did not find any association between *HER2/Neu* and *ETV4* in a clinical study [156]. Therefore, whether *ETV4* could act as a prognostic target or therapeutic agent for breast cancer, prostate cancer, and ovarian cancer requires further exploration.

The antitumor effect of the PEA3 subfamily was also found in several other tumors. *ETV1* is considered to be the downstream target of *miR-17*, an oncogene associated with cell motility. Therefore, overexpression of *miR-17* could enhance melanoma cell motility by inhibiting *ETV1* expression [77]. *ETV4* was also found to

Table 1. PEA3 subfamily mediates chemotherapy resistance in cancer

Major gene	Cancer type	PEA3 member	Drug	Mechanism
CIC	BRAF-mutated multiple myeloma	ETV4/5	Dabrafenib, trametinib	Mediated by CIC inactivation, ETV4/5 contributes to dabrafenib and trametinib resistance in BRAF-mutated multiple myeloma cells.
CIC	T-ALL	ETV4	Trametinib	CIC inactivation induces chemotherapy resistance to MAPK inhibition. ETV4 is the main downstream target of CIC in human T-ALL cells.
CIC	Pancreatic cancer	ETV1/4/5	Trametinib	Deletion of ATXN1L induces chemotherapy resistance by reducing CIC protein levels and restoring expression of ETV1, ETV4, and ETV5.
CIC	NSCLC	ETV1	Gefitinib	CIC suppresses the effects of EGFR inhibition by partially restoring the expression of ETV1.
CIC	Colorectal cancer	ETV5	Cetuximab	ETV5 is a potential target to overcome cetuximab resistance. Knockdown of ETV5 increases cetuximab sensitivity in KRAS WT cells.
CIC	Ovarian cancer	ETV4/5	Paclitaxel	ETV4 and ETV5 are upregulated by the miR-1307/CIC axis, which contributes to chemotherapy resistance.
COP1, DET1	GIST	ETV1/4/5	Imatinib, PD325901	By stabilizing ETV1/ETV4/ETV5 protein, COP1 and DET1 loss results in chemotherapy resistance in GIST and melanoma.
	Melanoma	ETV1/4/5	Vemurafenib	
IER3	HCC	ETV4	Sorafenib and cisplatin	ETV4 promotes sorafenib or cisplatin resistance in HCC by upregulating IER3, an oncogene related to chemotherapy resistance.
CDK6	Melanoma	ETV5	Vemurafenib	CDK6-mediated resistance to BRAF inhibition is collaboratively regulated by JUN and ETV5.
MDR1	Gastric cancer	ETV4	Vincristine	ETV4 upregulates MDR1 expression by binding to the promoter region of MDR1.

T-ALL, T-cell lymphoblastic lymphoma; NSCLC, non-small-cell lung cancer; EGFR, epidermal growth factor receptor; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; WT, wild type; MDR1, multi-drug resistance protein 1.

inhibit SiHa cervical cancer cell invasion: *ETV4* could activate the promotor of squamous cell carcinoma antigen, a serine proteinase inhibitor that may suppress cancer invasiveness, thus inhibiting cancer metastasis [157]. In addition, *ETV4* increased the expression of pro-apoptotic protein Bax and enhanced mithramycin A-induced Huh-7 cell apoptosis, supporting *ETV4* as an adjunctive therapeutic agent for mithramycin A in HCC [158].

Owing to these controversies, whether the PEA3 subfamily inhibits or promotes cancer progression in these tumor cells needs further validation.

Clinical significance of the PEA3 subfamily

The PEA3 subfamily is significantly correlated with distant metastasis of tumors and is considered to be an independent adverse prognostic factor. Of the PEA3 subfamily members, the *ETV1* transcription factor was the most frequently expressed in prostate cancer and high *ETV1* levels are associated with shorter time to prostate-specific antigen recurrence [159]. *ETV4* overexpression is correlated with depth of invasion, lymph node metastasis, and advanced pTNM stage in colorectal cancer, which indicated that *ETV4* could act as a prognostic marker in CRC progression and metastasis [160, 161]. As an oncogenic transcription factor, *ETV5* is an independent predictor for the prognosis of HCC patients [162]. This was also shown to be the case for triple-negative breast cancer [163, 164], gastric cancer [165], lung cancer [64], OSCC [166] and GBM [78], in which *ETV1*, *ETV4* and *ETV5* were positively associated with advanced stage, depth of invasion, lymph node metastasis and recurrence, resulting in shorter overall survival, disease-free survival, and relapse-free survival of patients. Consequently, all of these studies highlight the prognostic value of *ETV1*, *ETV4* and *ETV5*.

In addition to its prognostic value, the PEA3 subfamily also has a role in the clinical diagnosis of several cancers. *CIC*-rearranged sarcomas (which usually refers to *CIC-DUX4* gene fusion sarcomas) are a small subset of primitive round-cell sarcomas, which are difficult to diagnose and classify owing to the similarity between their characteristics and those of other small round cell sarcomas [167]. It has been reported that *ETV1/ETV4/ETV5* triple-positivity could be helpful for the identification of *CIC*-rearranged sarcomas [168]. Interestingly, *ETV1/ETV4/ETV5* overexpression was more reliable and sensitive than RNA sequencing and fluorescence in situ hybridization for diagnosing CIC-rearranged sarcomas [169]. In addition, compared with other PEA3 subfamily members, *ETV4* seems to be more effective for diagnosis because of its high sensitivity and specificity [170]. Detecting gene fusions can also be beneficial for diagnosis of other cancers. For instance, the *TMPRSS2-ERG* (53.1%) and *TMPRSS2-ETV1* (6.3%) gene fusions can be used as diagnostic tools for prostate cancer [171], whereas *EWS-ETV4* gene fusion can be used to diagnose Ewing's sarcoma [172].

Molecules and drugs targeting the PEA3 subfamily

Generally, inhibition of the MAPK signaling pathway can reduce the expression of the PEA3 subfamily to some extent. However, some factors (such as *CIC* mutation) allow the level of the PEA3 subfamily to be maintained independently of the MAPK pathway, which finally results in chemotherapy resistance. Thus, there is an urgent need to target the PEA3 subfamily.

As discussed above, several miRNAs (*miR-129-5p*, *miR-1224-3p*, *miR-195-5p*, *miR-582-5p*, *miR-17-5p*, *miR-17/20a*, and *miR-8067*) have been reported to directly target *ETV1* and *ETV5*. These miRNAs are potential therapeutic targets in *ETV1/ETV5*-overexpressing tumors. However, no miRNA that targets *ETV4* transcription factor has yet been reported. Therefore, identifying new miRNAs that target the PEA3 subfamily in different tumor types may help in the search for therapeutic targets.

Compounds that target the ETS proteins have been investigated as potential treatments for ETS-directed cancer [173]. YK-4-279, a small-molecule inhibitor of *EWS-FLI1*, *ERG*, and *ETV1*, has been found to significantly inhibit tumor growth and metastasis in *ETV1* fusion-positive prostate cancer; this result was validated at both cell and animal levels [174, 175]. Besides, a combination of YK-4-279 and low-dose docetaxel synergistically inhibited the proliferation and migration of prostate cancer cells. Importantly, this combination allowed the systemic toxicity caused by high doses of docetaxel to be avoided [176].

BRD32048 is another inhibitor of *ETV1* screened by small-molecule microarray, which has become a new therapeutic drug for *ETV1*-positive cancers. For example, BRD32048 inhibited the transcriptional activity of *ETV1* and cell invasion by directly binding to *ETV1* in *ETV1*-dependent prostate cancer cells [177]. Confusingly, research in neuroblastoma found that YK-4-279 significantly reduced cell growth and promoted cell apoptosis, whereas BRD-32048 did not [178]. It was further shown that YK-4-279 triggered cell apoptosis through inhibiting mitotic progression instead of regulating *ETV1* transcription activity, indicating that the anticancer effects of YK-4-279 are independent of the RAS-MEK/ERK-ETS(*ETV1*) axis in neuroblastoma cells [178].

Tamoxifen, a selective estrogen receptor modifier, was found to decrease *ETV4* and *ETV5* mRNA expression in benign breast tissues, suggesting that it is an effective agent to reduce breast cancer risk [179].

A recent study of GIST identified several possible ETV1 targeting drugs, among which trifluoperazine and thioridazine were considered to have strong anticancer effects, especially when combined with a MEK inhibitor [180].

Compared with synthetic drugs, phytochemicals have low toxicity and fewer side effects. Therefore, Nath et al. characterized p-anisidine, a plant compound inhibiting ETV1 expression, which shows promiscuous anticancer activity in human cervical carcinoma HeLa cells [181].

In general, YK-4-279, BRD3208, tamoxifen, trifluoperazine, thioridazine and p-anisidine are potential drugs targeting the PEA3 family, but their lack of specificity could cause off-target effects in patients [182]. In addition, oncogenic transcription factors are often considered to be

undruggable; therefore, developing new drugs that target the PEA3 subfamily remains challenging [177]. The miRNAs and drugs that target the PEA3 subfamily are shown in Table S2.

Conclusions and future perspectives

Overexpression of the PEA3 subfamily has been reported in many different cancer types and is significantly correlated with the malignant potential of tumors. However, some studies have found that members of the PEA3 subfamily could inhibit cell growth and promote apoptosis, indicating that they could also act as tumor suppressors. This discrepancy may be attributed to the fact that different cell lines were employed in these studies. In addition, overexpression of PEA3 subfamily members may be accompanied by an increase in the expression of other ETS genes, some of which are tumor suppressors, such as *ELF1*.

By systematically analyzing the activation mechanisms and biological functions of the PEA3 subfamily, we concluded that it could be activated by a series of genes and pathways: activation of the MAPK signaling pathway and the PI3K/Akt signaling pathway; loss of PEA3 repressors (*CIC*, *COP1*, and *DET1*); gene fusions induced by chromosome rearrangement; and miRNA-mediated post-transcriptional regulation. Many investigations have shown that the PEA3 subfamily contributes to cancer progression and metastasis by regulating several biological processes, including cell growth, apoptosis, EMT, cell migration and invasion, cell stemness, and chemotherapy resistance.

Chemotherapy resistance is the main cause of cancer recurrence and treatment failure. We note that *ETV1*, *ETV4*, and *ETV5* are located downstream of MAPK and PI3K/Akt signaling; thus, MAPK inhibitors and PI3K/Akt inhibitors are available for the treatment of *ETV1/ETV4/ETV5*-overexpressing tumors. However, inhibition of these two pathways alone is not enough to keep expression of the PEA3 subfamily at a low level owing to *CIC/COP1/DET1* deficiency-induced PEA3 subfamily recovery, which leads to drug resistance against the MAPK inhibitor and the PI3K/Akt inhibitor. In order to reduce drug resistance, combined targeting of the MAPK signaling pathway and the PEA3 subfamily may be considered in the future. However, directly targeting transcription factors is challenging. Up to now, only YK-4-279, BRD3208, tamoxifen, trifluoperazine, thioridazine, and p-anisidine have been reported to target the PEA3 subfamily. Therefore, developing new drugs that target the PEA3 subfamily may greatly improve cancer therapy in the future.

CSCs generally correlate with tumor metastasis, resistance, and recurrence owing to their strong tumorigenic ability. Several studies have linked the PEA3 subfamily to CSC characteristics, indicating that the PEA3 subfamily may contribute to the maintenance of CSC characteristics. However, the mechanisms by which the PEA3 subfamily promotes stem cell properties is unclear, and there has been very limited research on the PEA3 subfamily and CSC. Thus, there is a need for in vitro and in vivo experiments in specific tumor types to further investigate whether the PEA3 subfamily promotes CSC phenotypes and how it regulates CSC characteristics. CSCs are now an urgent topic in cancer research, targeting these cells seems to represent an effective therapy for patients with metastatic tumors.

Several miRNAs can directly bind to the 3'-UTR of *ETV1* and *ETV5* to inhibit *ETV1/ETV5* expression and reduce cell growth. However, no miRNA that targets *ETV4* has yet been reported. *ETV4* is closely related to a more aggressive tumor phenotype and is repeatedly activated in advanced and metastatic tumors. Besides, *ETV4* is known to be an independent and unfavorable prognostic indicator in cancer patients. Therefore, exploring miRNAs that directly target *ETV4* for use in cancer therapy should be a priority in future research.

Cis-regulatory elements (CREs), including enhancers, usually have strong regulatory effects on tumors. Recently, a mutant CRE was found to interact with the *ETV1* promoter to induce overexpression of *ETV1*, leading to poor prognosis in CRC patients [183]. As an oncogenic transcription factor, *ETV4* directly binds the 5' and 3' *MYC* enhancers and increases *MYC* expression in prostate cancer. Besides, *ETV4* and transcriptional cofactor mediator subunit 25 (MED25) could occupy enhancers to promote the expression of *ETV4* target genes in prostate cancer cells [184]. These results indicate that the PEA3 subfamily may occupy enhancer sites to regulate the expression of genes closely related to cancer progression.

Oncogenic transcription factors are usually enriched in the enhancer region, especially the super-enhancer region, to regulate gene expression. Therefore, whether ETV1, *ETV4*, and *ETV5* transcription factors occupy super-enhancer sites to mediate key oncogene expression is worth exploring.

In summary, deregulation of the PEA3 subfamily usually promotes tumor growth, progression, resistance, and metastasis by inducing EMT, regulating the expression of invasion/migration-related genes, and maintaining CSC characteristics. Therefore, targeting *ETV1/ETV4/ETV5*-related genes or pathways may provide effective therapeutic regimens for cancer in the future. Besides, as oncogenic transcription factors, *ETV1*, *ETV4*, and *ETV5* may serve as useful biological markers for tumor diagnosis and prognosis.

Acknowledgements

The study was supported by the grant of the Hunan Provincial Department of Finance (No. 2019-93, No. 2018-92).

Disclosure of conflict of interest

None.

Abbreviations

ACC1, Acetyl-CoA carboxylase; ACLY, ATP citrate lyase; ALK, Anaplastic lymphoma kinase; ASXL1, Additional sex combs-like 1; BDNF, Brain-derived neurotrophic factor; CHK1, Checkpoint kinase 1; CIC, Capicua; COP1, Constitutive photomorphogenetic 1; CRC, Colorectal cancer; CRE, Cis-regulatory element; CSC, Cancer stem cell; DBC1, Deleted in Breast Cancer 1; Dppa4, Developmental pluripotency associated factor 4; EMT, Epithelial-mesenchymal transition; ETS, E26 transformation-specific; FGFR3, Fibroblast growth factor receptor 3; GBM, Glioblastoma; GIST, Gastrointestinal stromal tumor; HCC, Hepatocellular carcinoma; HGF, Hepatocyte growth factor; HHEX, Hematopoietically Expressed Homeobox; LAUD, Lung adenocarcinoma; MAP3K8, Mitogen-activated protein kinase kinase kinase 8; MAPK, Mitogen-activated protein kinase; MCAM, Melanoma cell adhesion molecule; MDR1, Multi-drug resistance protein 1; MED25, Mediator subunit 25; miRNA, microRNAs; MMP, Matrix metalloproteinase; NRP2, Neuropilin 2; NSCLC, Non-small-cell lung cancer; OSCC, Oral squamous cell carcinoma; PBK, PDZ-binding kinase; PTGS2, Cyclooxygenase-2; RCC, Renal cell carcinoma; RTK, Receptor tyrosine kinase; SOX9, SRY-box9; SRSF3, Serine and arginine rich splicing factor 3; TGF-β, Transforming growth factor β; TMPRSS2, Transmembrane Serine Protease 2; UTR, Untranslated region.

Address correspondence to: Drs. Qiong Lu and Jian Qu, Department of Pharmacy, The Second Xiangya Hospital of Central South University, 139 Middle Renmin Road, Changsha 410011, Hunan, PR China. Tel: +86-731-85292072; Fax: +86-731-85533525; E-mail: christy_luq@csu.edu.cn (QL); qujianstanley@csu.edu.cn (JQ)

References

[1] Oh S, Shin S and Janknecht R. ETV1, 4 and 5: an oncogenic subfamily of ETS transcription factors. Biochim Biophys Acta 2012; 1826: 1-12.

[2] Nicholas TR, Strittmatter BG and Hollenhorst PC. Oncogenic ETS factors in prostate cancer. Adv Exp Med Biol 2019; 1210: 409-436.

[3] Clark JP and Cooper CS. ETS gene fusions in prostate cancer. Nat Rev Urol 2009; 6: 429-439.

[4] Sementchenko VI and Watson DK. Ets target genes: past, present and future. Oncogene 2000; 19: 6533-6548.

[5] de Launoit Y, Chotteau-Lelievre A, Beaudoin C, Coutte L, Netzer S, Brenner C, Huvent I and Baert JL. The PEA3 group of ETS-related transcription factors. Role in breast cancer metastasis. Adv Exp Med Biol 2000; 480: 107-116.

[6] Wang B, Krall EB, Aguirre AJ, Kim M, Widlund HR, Doshi MB, Sicinska E, Sulahian R, Goodale A, Cowley GS, Piccioni F, Doench JG, Root DE and Hahn WC. ATXN1L, CIC, and ETS transcription factors modulate sensitivity to mapk pathway inhibition. Cell Rep 2017; 18: 1543-1557.

[7] Morsalin S, Yang C, Fang J, Reddy S, Kayarthodi S, Childs E, Matthews R, Rao VN and Reddy ESP. Molecular mechanism of β-Catenin signaling pathway inactivation in ETV1-Positive prostate cancers. J Pharm Sci Pharmacol 2015; 2: 208-216.

[8] Eid W and Abdel-Rehim W. Genome-wide analysis of ETV1 targets: insights into the role of ETV1 in tumor progression. J Cell Biochem 2019; 120: 8983-8991.

[9] Jang BG, Lee HE and Kim WH. ETV1 mRNA is specifically expressed in gastrointestinal stromal tumors. Virchows Arch 2015; 467: 393-403.

[10] Zhang X, Wang Y, Liu X, Zhao A, Yang Z, Kong F, Sun L, Yu Y and Jiang L. KIF2A promotes the

progression via AKT signaling pathway and is upregulated by transcription factor ETV4 in human gastric cancer. Biomed Pharmacother 2020; 125: 109840.
[11] Cheng T, Zhang Z, Cheng Y, Zhang J, Tang J, Tan Z, Liang Z, Chen T, Liu Z, Li J, Zhao J and Zhou R. ETV4 promotes proliferation and invasion of lung adenocarcinoma by transcriptionally upregulating MSI2. Biochem Biophys Res Commun 2019; 516: 278-284.
[12] Yang QX, Zhong S, He L, Jia XJ, Tang H, Cheng ST, Ren JH, Yu HB, Zhou L, Zhou HZ, Ren F, Hu ZW, Gong R, Huang AL and Chen J. PBK overexpression promotes metastasis of hepatocellular carcinoma via activating ETV4-uPAR signaling pathway. Cancer Lett 2019; 452: 90-102.
[13] Mesci A, Taeb S, Huang X, Jairath R, Sivaloganathan D and Liu SK. Pea3 expression promotes the invasive and metastatic potential of colorectal carcinoma. World J Gastroenterol 2014; 20: 17376-17387.
[14] Pedrola N, Devis L, Llauradó M, Campoy I, Martinez-Garcia E, Garcia M, Muinelo-Romay L, Alonso-Alconada L, Abal M, Alameda F, Mancebo G, Carreras R, Castellví J, Cabrera S, Gil-Moreno A, Matias-Guiu X, Iovanna JL, Colas E, Reventós J and Ruiz A. Nidogen 1 and nuclear protein 1: novel targets of ETV5 transcription factor involved in endometrial cancer invasion. Clin Exp Metastasis 2015; 32: 467-478.
[15] Llauradó M, Majem B, Castellví J, Cabrera S, Gil-Moreno A, Reventós J and Ruiz A. Analysis of gene expression regulated by the ETV5 transcription factor in OV90 ovarian cancer cells identifies FOXM1 overexpression in ovarian cancer. Mol Cancer Res 2012; 10: 914-924.
[16] de Launoit Y, Baert JL, Chotteau A, Monte D, Defossez PA, Coutte L, Pelczar H and Leenders F. Structure-function relationships of the PEA3 group of Ets-related transcription factors. Biochem Mol Med 1997; 61: 127-135.
[17] Chotteau-Lelièvre A, Desbiens X, Pelczar H, Defossez PA and de Launoit Y. Differential expression patterns of the PEA3 group transcription factors through murine embryonic development. Oncogene 1997; 15: 937-952.
[18] Currie SL, Lau DKW, Doane JJ, Whitby FG, Okon M, McIntosh LP and Graves BJ. Structured and disordered regions cooperatively mediate DNA-binding autoinhibition of ETS factors ETV1, ETV4 and ETV5. Nucleic Acids Res 2017; 45: 2223-2241.
[19] Shekhar A, Lin X, Liu FY, Zhang J, Mo H, Bastarache L, Denny JC, Cox NJ, Delmar M, Roden DM, Fishman GI and Park DS. Transcription factor ETV1 is essential for rapid conduction in the heart. J Clin Invest 2016; 126: 4444-4459.
[20] Rommel C, Rösner S, Lother A, Barg M, Schwaderer M, Gilsbach R, Bömicke T, Schnick T, Mayer S, Doll S, Hesse M, Kretz O, Stiller B, Neumann FJ, Mann M, Krane M, Fleischmann BK, Ravens U and Hein L. The transcription factor ETV1 induces atrial remodeling and arrhythmia. Circ Res 2018; 123: 550-563.
[21] Fatkin D. ETV1: a new player in atrial remodeling. Circ Res 2018; 123: 515-517.
[22] Tenney AP, Livet J, Belton T, Prochazkova M, Pearson EM, Whitman MC, Kulkarni AB, Engle EC and Henderson CE. Etv1 controls the establishment of non-overlapping motor innervation of neighboring facial muscles during development. Cell Rep 2019; 29: 437-452, e434.
[23] Abe H, Okazawa M and Nakanishi S. Gene regulation via excitation and BDNF is mediated by induction and phosphorylation of the Etv1 transcription factor in cerebellar granule cells. Proc Natl Acad Sci U S A 2012; 109: 8734-8739.
[24] Okazawa M, Abe H and Nakanishi S. The Etv1 transcription factor activity-dependently downregulates a set of genes controlling cell growth and differentiation in maturing cerebellar granule cells. Biochem Biophys Res Commun 2016; 473: 1071-1077.
[25] Yang JJ, Bertolesi GE, Hehr CL and McFarlane S. Lhx2/9 and Etv1 transcription factors have complementary roles in regulating the expression of guidance genes slit1 and sema3a. Neuroscience 2020; 434: 66-82.
[26] Iwata T, Mizuno N, Nagahara T, Kaneda-Ikeda E, Kajiya M, Kitagawa M, Takeda K, Yoshioka M, Yagi R, Takata T and Kurihara H. Identification of regulatory mRNA and microRNA for differentiation into cementoblasts and periodontal ligament cells. J Periodontal Res 2020; [Epub ahead of print].
[27] Fontanet PA, Ríos AS, Alsina FC, Paratcha G and Ledda F. Pea3 transcription factors, Etv4 and Etv5, are required for proper hippocampal dendrite development and plasticity. Cereb Cortex 2018; 28: 236-249.
[28] Liu D, Liu Z, Liu H, Li H, Pan X and Li Z. Brain-derived neurotrophic factor promotes vesicular glutamate transporter 3 expression and neurite outgrowth of dorsal root ganglion neurons through the activation of the transcription factors Etv4 and Etv5. Brain Res Bull 2016; 121: 215-226.
[29] Fontanet P, Irala D, Alsina FC, Paratcha G and Ledda F. Pea3 transcription factor family members Etv4 and Etv5 mediate retrograde signaling and axonal growth of DRG sensory neurons in response to NGF. J Neurosci 2013; 33: 15940-15951.
[30] Lu BC, Cebrian C, Chi X, Kuure S, Kuo R, Bates CM, Arber S, Hassell J, MacNeil L, Hoshi M, Jain S, Asai N, Takahashi M, Schmidt-Ott KM, Barasch J, D'Agati V and Costantini F. Etv4 and Etv5 are required downstream of GDNF and

Ret for kidney branching morphogenesis. Nat Genet 2009; 41: 1295-1302.
[31] Kuure S, Chi X, Lu B and Costantini F. The transcription factors Etv4 and Etv5 mediate formation of the ureteric bud tip domain during kidney development. Development 2010; 137: 1975-1979.
[32] Riccio P, Cebrian C, Zong H, Hippenmeyer S and Costantini F. Ret and Etv4 Promote directed movements of progenitor cells during renal branching morphogenesis. PLoS Biol 2016; 14: e1002382.
[33] Alankarage D, Lavery R, Svingen T, Kelly S, Ludbrook L, Bagheri-Fam S, Koopman P and Harley V. SOX9 regulates expression of the male fertility gene Ets variant factor 5 (ETV5) during mammalian sex development. Int J Biochem Cell Biol 2016; 79: 41-51.
[34] Morrow CM, Hostetler CE, Griswold MD, Hofmann MC, Murphy KM, Cooke PS and Hess RA. ETV5 is required for continuous spermatogenesis in adult mice and may mediate blood testes barrier function and testicular immune privilege. Ann N Y Acad Sci 2007; 1120: 144-151.
[35] Eo J, Han K, K MM, Song H and Lim HJ. Etv5, an ETS transcription factor, is expressed in granulosa and cumulus cells and serves as a transcriptional regulator of the cyclooxygenase-2. J Endocrinol 2008; 198: 281-290.
[36] Zhang X, Wei R, Sun Y, Xia Q, Xie W, Song H, Wang W and Zou K. AKT3 is a pivotal molecule of Cadherin-22 and GDNF Family receptor-α1 signal pathways regulating self-renewal in female germline stem cells. Stem Cells 2019; 37: 1095-1107.
[37] Jamsai D, Clark BJ, Smith SJ, Whittle B, Goodnow CC, Ormandy CJ and O'Bryan MK. A missense mutation in the transcription factor ETV5 leads to sterility, increased embryonic and perinatal death, postnatal growth restriction, renal asymmetry and polydactyly in the mouse. PLoS One 2013; 8: e77311.
[38] Gutierrez-Aguilar R, Thompson A, Marchand N, Dumont P, Woods SC, de Launoit Y, Seeley RJ and Ulrich-Lai YM. The obesity-associated transcription factor ETV5 modulates circulating glucocorticoids. Physiol Behav 2015; 150: 38-42.
[39] Gutierrez-Aguilar R, Kim DH, Casimir M, Dai XQ, Pfluger PT, Park J, Haller A, Donelan E, Park J, D'Alessio D, Woods SC, MacDonald PE and Seeley RJ. The role of the transcription factor ETV5 in insulin exocytosis. Diabetologia 2014; 57: 383-391.
[40] Degirmenci U, Wang M and Hu J. Targeting aberrant RAS/RAF/MEK/ERK signaling for cancer therapy. Cells 2020; 9: 198.
[41] Bunda S, Heir P, Li ASC, Mamatjan Y, Zadeh G and Aldape K. c-Src phosphorylates and inhibits the function of the cic tumor suppressor protein. Mol Cancer Res 2020; 18: 774-786.
[42] Chi P, Chen Y, Zhang L, Guo X, Wongvipat J, Shamu T, Fletcher JA, Dewell S, Maki RG, Zheng D, Antonescu CR, Allis CD and Sawyers CL. ETV1 is a lineage survival factor that cooperates with KIT in gastrointestinal stromal tumours. Nature 2010; 467: 849-853.
[43] Ran L, Sirota I, Cao Z, Murphy D, Chen Y, Shukla S, Xie Y, Kaufmann MC, Gao D, Zhu S, Rossi F, Wongvipat J, Taguchi T, Tap WD, Mellinghoff IK, Besmer P, Antonescu CR, Chen Y and Chi P. Combined inhibition of MAP kinase and KIT signaling synergistically destabilizes ETV1 and suppresses GIST tumor growth. Cancer Discov 2015; 5: 304-315.
[44] Duensing A. Targeting ETV1 in gastrointestinal stromal tumors: tripping the circuit breaker in GIST? Cancer Discov 2015; 5: 231-233.
[45] Wang HC, Li TY, Chao YJ, Hou YC, Hsueh YS, Hsu KH and Shan YS. KIT exon 11 codons 557-558 deletion mutation promotes liver metastasis through the CXCL12/CXCR4 axis in gastrointestinal stromal tumors. Clin Cancer Res 2016; 22: 3477-3487.
[46] Hayashi Y, Bardsley MR, Toyomasu Y, Milosavljevic S, Gajdos GB, Choi KM, Reid-Lombardo KM, Kendrick ML, Bingener-Casey J, Tang CM, Sicklick JK, Gibbons SJ, Farrugia G, Taguchi T, Gupta A, Rubin BP, Fletcher JA, Ramachandran A and Ordog T. Platelet-derived growth factor receptor-α regulates proliferation of gastrointestinal stromal tumor cells with mutations in KIT by stabilizing ETV1. Gastroenterology 2015; 149: 420-432, e416.
[47] Tan J, Yang S, Shen P, Sun H, Xiao J, Wang Y, Wu B, Ji F, Yan J, Xue H and Zhou D. C-kit signaling promotes proliferation and invasion of colorectal mucinous adenocarcinoma in a murine model. Oncotarget 2015; 6: 27037-27048.
[48] Kherrouche Z, Monte D, Werkmeister E, Stoven L, De Launoit Y, Cortot AB, Tulasne D and Chotteau-Lelievre A. PEA3 transcription factors are downstream effectors of Met signaling involved in migration and invasiveness of Met-addicted tumor cells. Mol Oncol 2015; 9: 1852-1867.
[49] Bunda S, Heir P, Metcalf J, Li ASC, Agnihotri S, Pusch S, Yasin M, Li M, Burrell K, Mansouri S, Singh O, Wilson M, Alamsahebpour A, Nejad R, Choi B, Kim D, von Deimling A, Zadeh G and Aldape K. CIC protein instability contributes to tumorigenesis in glioblastoma. Nat Commun 2019; 10: 661.
[50] Chen Y, Sumardika IW, Tomonobu N, Winarsa Ruma IM, Kinoshita R, Kondo E, Inoue Y, Sato H, Yamauchi A, Murata H, Yamamoto KI, Tomida S, Shien K, Yamamoto H, Soh J, Liu M, Futami J, Sasai K, Katayama H, Kubo M, Putranto

EW, Hibino T, Sun B, Nishibori M, Toyooka S and Sakaguchi M. Melanoma cell adhesion molecule is the driving force behind the dissemination of melanoma upon S100A8/A9 binding in the original skin lesion. Cancer Lett 2019; 452: 178-190.

[51] Chen Y, Sumardika IW, Tomonobu N, Kinoshita R, Inoue Y, Iioka H, Mitsui Y, Saito K, Ruma IMW, Sato H, Yamauchi A, Murata H, Yamamoto KI, Tomida S, Shien K, Yamamoto H, Soh J, Futami J, Kubo M, Putranto EW, Murakami T, Liu M, Hibino T, Nishibori M, Kondo E, Toyooka S and Sakaguchi M. Critical role of the MCAM-ETV4 axis triggered by extracellular S100A8/A9 in breast cancer aggressiveness. Neoplasia 2019; 21: 627-640.

[52] Lemaître C, Tsang J, Bireau C, Heidmann T and Dewannieux M. A human endogenous retrovirus-derived gene that can contribute to oncogenesis by activating the ERK pathway and inducing migration and invasion. PLoS Pathog 2017; 13: e1006451.

[53] Andradas C, Blasco-Benito S, Castillo-Lluva S, Dillenburg-Pilla P, Diez-Alarcia R, Juanes-García A, García-Taboada E, Hernando-Llorente R, Soriano J, Hamann S, Wenners A, Alkatout I, Klapper W, Rocken C, Bauer M, Arnold N, Quintanilla M, Megías D, Vicente-Manzanares M, Urigüen L, Gutkind JS, Guzmán M, Pérez-Gómez E and Sánchez C. Activation of the orphan receptor GPR55 by lysophosphatidylinositol promotes metastasis in triple-negative breast cancer. Oncotarget 2016; 7: 47565-47575.

[54] Mus LM, Lambertz I, Claeys S, Kumps C, Van Loocke W, Van Neste C, Umapathy G, Vaapil M, Bartenhagen C, Laureys G, De Wever O, Bexell D, Fischer M, Hallberg B, Schulte J, De Wilde B, Durinck K, Denecker G, De Preter K and Speleman F. The ETS transcription factor ETV5 is a target of activated ALK in neuroblastoma contributing to increased tumour aggressiveness. Sci Rep 2020; 10: 218.

[55] di Martino E, Alder O, Hurst CD and Knowles MA. ETV5 links the FGFR3 and Hippo signalling pathways in bladder cancer. Sci Rep 2019; 9: 5740.

[56] Fung TM, Ng KY, Tong M, Chen JN, Chai S, Chan KT, Law S, Lee NP, Choi MY, Li B, Cheung AL, Tsao SW, Qin YR, Guan XY, Chan KW and Ma S. Neuropilin-2 promotes tumourigenicity and metastasis in oesophageal squamous cell carcinoma through ERK-MAPK-ETV4-MMP-E-cadherin deregulation. J Pathol 2016; 239: 309-319.

[57] Wong D and Yip S. Making heads or tails - the emergence of capicua (CIC) as an important multifunctional tumour suppressor. J Pathol 2020; 250: 532-540.

[58] Simón-Carrasco L, Graña O, Salmón M, Jacob HKC, Gutierrez A, Jiménez G, Drosten M and Barbacid M. Inactivation of capicua in adult mice causes T-cell lymphoblastic lymphoma. Genes Dev 2017; 31: 1456-1468.

[59] Lee JS, Kim E, Lee J, Kim D, Kim H, Kim CJ, Kim S, Jeong D and Lee Y. Capicua suppresses colorectal cancer progression via repression of ETV4 expression. Cancer Cell Int 2020; 20: 42.

[60] Zhou Y, Wang M, Shuang T, Liu Y, Zhang Y and Shi C. MiR-1307 influences the chemotherapeutic sensitivity in ovarian cancer cells through the regulation of the CIC transcriptional repressor. Pathol Res Pract 2019; 215: 152606.

[61] Yoe J, Kim D, Kim S and Lee Y. Capicua restricts cancer stem cell-like properties in breast cancer cells. Oncogene 2020; 39: 3489-3506.

[62] Da Già MC, Solimando AG, Garitano-Trojaola A, Barrio S, Munawar U, Strifler S, Haertle L, Rhodes N, Teufel E, Vogt C, Lapa C, Beilhack A, Rasche L, Einsele H and Kortüm KM. CIC mutation as a molecular mechanism of acquired resistance to combined BRAF-MEK inhibition in extramedullary multiple myeloma with central nervous system involvement. Oncologist 2020; 25: 112-118.

[63] Kim E, Kim D, Lee JS, Yoe J, Park J, Kim CJ, Jeong D, Kim S and Lee Y. Capicua suppresses hepatocellular carcinoma progression by controlling the ETV4-MMP1 axis. Hepatology 2018; 67: 2287-2301.

[64] Okimoto RA, Breitenbuecher F, Olivas VR, Wu W, Gini B, Hofree M, Asthana S, Hrustanovic G, Flanagan J, Tulpule A, Blakely CM, Haringsma HJ, Simmons AD, Gowen K, Suh J, Miller VA, Ali S, Schuler M and Bivona TG. Inactivation of Capicua drives cancer metastasis. Nat Genet 2017; 49: 87-96.

[65] Vitari AC, Leong KG, Newton K, Yee C, O'Rourke K, Liu J, Phu L, Vij R, Ferrando R, Couto SS, Mohan S, Pandita A, Hongo JA, Arnott D, Wertz IE, Gao WQ, French DM and Dixit VM. COP1 is a tumour suppressor that causes degradation of ETS transcription factors. Nature 2011; 474: 403-406.

[66] Baert JL, Monte D, Verreman K, Degerny C, Coutte L and de Launoit Y. The E3 ubiquitin ligase complex component COP1 regulates PEA3 group member stability and transcriptional activity. Oncogene 2010; 29: 1810-1820.

[67] Xie Y, Cao Z, Wong EW, Guan Y, Ma W, Zhang JQ, Walczak EG, Murphy D, Ran L, Sirota I, Wang S, Shukla S, Gao D, Knott SR, Chang K, Leu J, Wongvipat J, Antonescu CR, Hannon G, Chi P and Chen Y. COP1/DET1/ETS axis regulates ERK transcriptome and sensitivity to MAPK inhibitors. J Clin Invest 2018; 128: 1442-1457.

[68] Ta L, Xuan C, Xing N and Zhu X. COP1 is downregulated in renal cell carcinoma (RCC) and inhibits the migration of RCC ACHN cells in vitro. Mol Med Rep 2016; 14: 1371-1378.
[69] Ouyang M, Wang H, Ma J, Lü W, Li J, Yao C, Chang G, Bi J, Wang S and Wang W. COP1, the negative regulator of ETV1, influences prognosis in triple-negative breast cancer. BMC Cancer 2015; 15: 132.
[70] Zeng S, Seifert AM, Zhang JQ, Kim TS, Bowler TG, Cavnar MJ, Medina BD, Vitiello GA, Rossi F, Loo JK, Param NJ and DeMatteo RP. ETV4 collaborates with Wnt/β-catenin signaling to alter cell cycle activity and promote tumor aggressiveness in gastrointestinal stromal tumor. Oncotarget 2017; 8: 114195-114209.
[71] Gao G, Xiu D, Yang B, Sun D, Wei X, Ding Y, Ma Y and Wang Z. miR-129-5p inhibits prostate cancer proliferation via targeting ETV1. Onco Targets Ther 2019; 12: 3531-3544.
[72] Zuo Y, Shen W, Wang C, Niu N and Pu J. Circular RNA Circ-ZNF609 promotes lung adenocarcinoma proliferation by modulating miR-1224-3p/ETV1 signaling. Cancer Manag Res 2020; 12: 2471-2479.
[73] Li H, Shen S, Ruan X, Liu X, Zheng J, Liu Y, Yang C, Wang D, Liu L, Ma J, Ma T, Wang P, Cai H, Li Z, Zhao L and Xue Y. Biosynthetic CircRNA_001160 induced by PTBP1 regulates the permeability of BTB via the CircRNA_001160/miR-195-5p/ETV1 axis. Cell Death Dis 2019; 10: 960.
[74] Jin X, Guan Y, Sheng H and Liu Y. Crosstalk in competing endogenous RNA network reveals the complex molecular mechanism underlying lung cancer. Oncotarget 2017; 8: 91270-91280.
[75] Li J, Lai Y, Ma J, Liu Y, Bi J, Zhang L, Chen L, Yao C, Lv W, Chang G, Wang S, Ouyang M and Wang W. miR-17-5p suppresses cell proliferation and invasion by targeting ETV1 in triple-negative breast cancer. BMC Cancer 2017; 17: 745.
[76] Gits CM, van Kuijk PF, Jonkers MB, Boersma AW, van Ijcken WF, Wozniak A, Sciot R, Rutkowski P, Schöffski P, Taguchi T, Mathijssen RH, Verweij J, Sleijfer S, Debiec-Rychter M and Wiemer EA. MiR-17-92 and miR-221/222 cluster members target KIT and ETV1 in human gastrointestinal stromal tumours. Br J Cancer 2013; 109: 1625-1635.
[77] Cohen R, Greenberg E, Nemlich Y, Schachter J and Markel G. miR-17 regulates melanoma cell motility by inhibiting the translation of ETV1. Oncotarget 2015; 6: 19006-19016.
[78] Wang H, Zhang H, Zeng J and Tan Y. ceRNA network analysis reveals prognostic markers for glioblastoma. Oncol Lett 2019; 17: 5545-5557.
[79] Rahim S and Uren A. Emergence of ETS transcription factors as diagnostic tools and therapeutic targets in prostate cancer. Am J Transl Res 2013; 5: 254-268.
[80] Gasi Tandefelt D, Boormans J, Hermans K and Trapman J. ETS fusion genes in prostate cancer. Endocr Relat Cancer 2014; 21: R143-152.
[81] Kumar-Sinha C, Tomlins SA and Chinnaiyan AM. Recurrent gene fusions in prostate cancer. Nat Rev Cancer 2008; 8: 497-511.
[82] Yun JW, Yang L, Park HY, Lee CW, Cha H, Shin HT, Noh KW, Choi YL, Park WY and Park PJ. Dysregulation of cancer genes by recurrent intergenic fusions. Genome Biol 2020; 21: 166.
[83] Torres A, Alshalalfa M, Tomlins SA, Erho N, Gibb EA, Chelliserry J, Lim L, Lam LLC, Faraj SF, Bezerra SM, Davicioni E, Yousefi K, Ross AE, Netto GJ, Schaeffer EM and Lotan TL. Comprehensive determination of prostate tumor ETS gene status in clinical samples using the CLIA decipher assay. J Mol Diagn 2017; 19: 475-484.
[84] Linn DE, Bronson RT and Li Z. Genetic interaction between Tmprss2-ERG gene fusion and Nkx3.1-loss does not enhance prostate tumorigenesis in mouse models. PLoS One 2015; 10: e0120628.
[85] Barros-Silva JD, Paulo P, Bakken AC, Cerveira N, Løvf M, Henrique R, Jerónimo C, Lothe RA, Skotheim RI and Teixeira MR. Novel 5' fusion partners of ETV1 and ETV4 in prostate cancer. Neoplasia 2013; 15: 720-726.
[86] Lu Z, Williamson SR, Carskadon S, Arachchige PD, Dhamdhere G, Schultz DS, Stricker H, Peabody JO, Jeong W, Chitale DA, Bismar TA, Rogers CG, Menon M, Gupta NS and Palanisamy N. Clonal evaluation of early onset prostate cancer by expression profiling of ERG, SPINK1, ETV1, and ETV4 on whole-mount radical prostatectomy tissue. Prostate 2020; 80: 38-50.
[87] Dedigama-Arachchige P, Carskadon S, Li J, Loveless I, Alhamar M, Peabody JO, Stricker H, Chitale DA, Rogers CG, Menon M, Gupta NS, Bismar TA, Williamson SR and Palanisamy N. Clonal evaluation of prostate cancer molecular heterogeneity in biopsy samples by dual immunohistochemistry and dual RNA in situ hybridization. Mod Pathol 2020; 33: 1791-1801.
[88] Qu X, Yeung C, Coleman I, Nelson PS and Fang M. Comparison of four next generation sequencing platforms for fusion detection: oncomine by ThermoFisher, AmpliSeq by illumina, FusionPlex by ArcherDX, and QIAseq by QIAGEN. Cancer Genet 2020; 243: 11-18.
[89] Yang J, Chen Y, Lu J, Wang X, Wang L, Liang J and Sun ZS. Identification and characterization of novel fusion genes in prostate cancer by targeted RNA capture and next-generation sequencing. Acta Biochim Biophys Sin (Shanghai) 2018; 50: 1166-1172.

[90] Delattre O. Ewing's tumours, genetic and cellular aspects. Pathol Biol (Paris) 2008; 56: 257-259.
[91] Specht K and Hartmann W. Ewing sarcomas and Ewing-like sarcomas : new aspects. Pathologe 2018; 39: 154-163.
[92] Tsuda Y, Zhang L, Meyers P, Tap WD, Healey JH and Antonescu CR. The clinical heterogeneity of round cell sarcomas with EWSR1/FUS gene fusions: impact of gene fusion type on clinical features and outcome. Genes Chromosomes Cancer 2020; 59: 525-534.
[93] Shulman SC, Katzenstein H, Bridge J, Bannister LL, Qayed M, Oskouei S and Shehata BM. Ewing sarcoma with 7;22 translocation: three new cases and clinicopathological characterization. Fetal Pediatr Pathol 2012; 31: 341-348.
[94] Takahashi A, Higashino F, Aoyagi M, Yoshida K, Itoh M, Kyo S, Ohno T, Taira T, Ariga H, Nakajima K, Hatta M, Kobayashi M, Sano H, Kohgo T and Shindoh M. EWS/ETS fusions activate telomerase in Ewing's tumors. Cancer Res 2003; 63: 8338-8344.
[95] Matjašič A, Zupan A, Boštjančič E, Pižem J, Popović M and Kolenc D. A novel PTPRZ1-ETV1 fusion in gliomas. Brain Pathol 2020; 30: 226-234.
[96] Xu L, Hu H, Zheng LS, Wang MY, Mei Y, Peng LX, Qiang YY, Li CZ, Meng DF, Wang MD, Liu ZJ, Li XJ, Huang BJ and Qian CN. ETV4 is a theranostic target in clear cell renal cell carcinoma that promotes metastasis by activating the pro-metastatic gene FOSL1 in a PI3K-AKT dependent manner. Cancer Lett 2020; 482: 74-89.
[97] Aytes A, Mitrofanova A, Kinkade CW, Lefebvre C, Lei M, Phelan V, LeKaye HC, Koutcher JA, Cardiff RD, Califano A, Shen MM and Abate-Shen C. ETV4 promotes metastasis in response to activation of PI3-kinase and Ras signaling in a mouse model of advanced prostate cancer. Proc Natl Acad Sci U S A 2013; 110: E3506-3515.
[98] Ran L, Chen Y, Sher J, Wong EWP, Murphy D, Zhang JQ, Li D, Deniz K, Sirota I, Cao Z, Wang S, Guan Y, Shukla S, Li KY, Chramiec A, Xie Y, Zheng D, Koche RP, Antonescu CR, Chen Y and Chi P. FOXF1 defines the core-regulatory circuitry in gastrointestinal stromal tumor. Cancer Discov 2018; 8: 234-251.
[99] Song X, Wan X, Huang T, Zeng C, Sastry N, Wu B, James CD, Horbinski C, Nakano I, Zhang W, Hu B and Cheng SY. SRSF3-regulated RNA alternative splicing promotes glioblastoma tumorigenicity by affecting multiple cellular processes. Cancer Res 2019; 79: 5288-5301.
[100] Hashimoto S, Furukawa S, Hashimoto A, Tsutaho A, Fukao A, Sakamura Y, Parajuli G, Onodera Y, Otsuka Y, Handa H, Oikawa T, Hata S, Nishikawa Y, Mizukami Y, Kodama Y, Murakami M, Fujiwara T, Hirano S and Sabe H. ARF6 and AMAP1 are major targets of KRAS and TP53 mutations to promote invasion, PD-L1 dynamics, and immune evasion of pancreatic cancer. Proc Natl Acad Sci U S A 2019; 116: 17450-17459.
[101] Jiang Y, Xu W, Lu J, He F and Yang X. Invasiveness of hepatocellular carcinoma cell lines: contribution of hepatocyte growth factor, c-met, and transcription factor Ets-1. Biochem Biophys Res Commun 2001; 286: 1123-1130.
[102] Hakuma N, Kinoshita I, Shimizu Y, Yamazaki K, Yoshida K, Nishimura M and Dosaka-Akita H. E1AF/PEA3 activates the Rho/Rho-associated kinase pathway to increase the malignancy potential of non-small-cell lung cancer cells. Cancer Res 2005; 65: 10776-10782.
[103] Hiroumi H, Dosaka-Akita H, Yoshida K, Shindoh M, Ohbuchi T, Fujinaga K and Nishimura M. Expression of E1AF/PEA3, an Ets-related transcription factor in human non-small-cell lung cancers: its relevance in cell motility and invasion. Int J Cancer 2001; 93: 786-791.
[104] Hanzawa M, Shindoh M, Higashino F, Yasuda M, Inoue N, Hida K, Ono M, Kohgo T, Nakamura M, Notani K, Fukuda H, Totsuka Y, Yoshida K and Fujinaga K. Hepatocyte growth factor upregulates E1AF that induces oral squamous cell carcinoma cell invasion by activating matrix metalloproteinase genes. Carcinogenesis 2000; 21: 1079-1085.
[105] Keenan MM, Liu B, Tang X, Wu J, Cyr D, Stevens RD, Ilkayeva O, Huang Z, Tollini LA, Murphy SK, Lucas J, Muoio DM, Kim SY and Chi JT. ACLY and ACC1 regulate hypoxia-induced apoptosis by modulating ETV4 via α-ketoglutarate. PLoS Genet 2015; 11: e1005599.
[106] Singsuksawat E, Thuwajit C, Charngkaew K and Thuwajit P. Increased ETV4 expression correlates with estrogen-enhanced proliferation and invasiveness of cholangiocarcinoma cells. Cancer Cell Int 2018; 18: 25.
[107] Klein RH, Tung PY, Somanath P, Fehling HJ and Knoepfler PS. Genomic functions of developmental pluripotency associated factor 4 (Dppa4) in pluripotent stem cells and cancer. Stem Cell Res 2018; 31: 83-94.
[108] Takeda R, Asada S, Park SJ, Yokoyama A, Becker HJ, Kanai A, Visconte V, Hershberger CE, Hayashi Y, Yonezawa T, Tamura M, Fukushima T, Tanaka Y, Fukuyama T, Matsumoto A, Yamasaki S, Nakai K, Yamazaki S, Inaba T, Shibata T, Inoue D, Honda H, Goyama S, Maciejewski JP and Kitamura T. HHEX promotes myeloid transformation in cooperation with mutant ASXL1. Blood 2020; 136: 1670-1684.

[109] Oh S, Shin S, Lightfoot SA and Janknecht R. 14-3-3 proteins modulate the ETS transcription factor ETV1 in prostate cancer. Cancer Res 2013; 73: 5110-5119.
[110] Khatiwada P, Kannan A, Malla M, Dreier M and Shemshedini L. Androgen up-regulation of Twist1 gene expression is mediated by ETV1. PeerJ 2020; 8: e8921.
[111] Arase M, Tamura Y, Kawasaki N, Isogaya K, Nakaki R, Mizutani A, Tsutsumi S, Aburatani H, Miyazono K and Koinuma D. Dynamics of chromatin accessibility during TGF-β-induced EMT of Ras-transformed mammary gland epithelial cells. Sci Rep 2017; 7: 1166.
[112] Kim HJ, Kim SH, Yu EJ, Seo WY and Kim JH. A positive role of DBC1 in PEA3-mediated progression of estrogen receptor-negative breast cancer. Oncogene 2015; 34: 4500-4508.
[113] Dowdy SC, Mariani A and Janknecht R. HER2/Neu- and TAK1-mediated up-regulation of the transforming growth factor beta inhibitor Smad7 via the ETS protein ER81. J Biol Chem 2003; 278: 44377-44384.
[114] Shin S, Bosc DG, Ingle JN, Spelsberg TC and Janknecht R. Rcl is a novel ETV1/ER81 target gene upregulated in breast tumors. J Cell Biochem 2008; 105: 866-874.
[115] Jørgensen CLT, Forsare C, Bendahl PO, Falck AK, Fernö M, Lövgren K, Aaltonen K and Rydén L. Expression of epithelial-mesenchymal transition-related markers and phenotypes during breast cancer progression. Breast Cancer Res Treat 2020; 181: 369-381.
[116] Nader JS, Guillon J, Petit C, Boissard A, Franconi F, Blandin S, Lambot S, Grégoire M, Verrièle V, Nawrocki-Raby B, Birembaut P, Coqueret O, Guette C and Pouliquen DL. S100A4 is a biomarker of tumorigenesis, EMT, invasion, and colonization of host organs in experimental malignant mesothelioma. Cancers (Basel) 2020; 12: 939.
[117] Wu QQ, Zhao M, Huang GZ, Zheng ZN, Chen Y, Zeng WS and Lv XZ. Fibroblast Activation Protein (FAP) overexpression induces Epithelial-Mesenchymal Transition (EMT) in oral squamous cell carcinoma by Down-Regulating Dipeptidyl Peptidase 9 (DPP9). Onco Targets Ther 2020; 13: 2599-2611.
[118] Yuen HF, Chan YK, Grills C, McCrudden CM, Gunasekharan V, Shi Z, Wong AS, Lappin TR, Chan KW, Fennell DA, Khoo US, Johnston PG and El-Tanani M. Polyomavirus enhancer activator 3 protein promotes breast cancer metastatic progression through snail-induced epithelial-mesenchymal transition. J Pathol 2011; 224: 78-89.
[119] Pellecchia A, Pescucci C, De Lorenzo E, Luceri C, Passaro N, Sica M, Notaro R and De Angioletti M. Overexpression of ETV4 is oncogenic in prostate cells through promotion of both cell proliferation and epithelial to mesenchymal transition. Oncogenesis 2012; 1: e20.
[120] Li Z, Zhang L, Ma Z, Yang M, Tang J, Fu Y, Mao Y, Hong X and Zhang Y. ETV1 induces epithelial to mesenchymal transition in human gastric cancer cells through the upregulation of Snail expression. Oncol Rep 2013; 30: 2859-2863.
[121] Puli OR, Danysh BP, McBeath E, Sinha DK, Hoang NM, Powell RT, Danysh HE, Cabanillas ME, Cote GJ and Hofmann MC. The transcription factor ETV5 mediates BRAFV600E-induced proliferation and TWIST1 expression in papillary thyroid cancer cells. Neoplasia 2018; 20: 1121-1134.
[122] Alonso-Alconada L, Eritja N, Muinelo-Romay L, Barbazan J, Lopez-Lopez R, Matias-Guiu X, Gil-Moreno A, Dolcet X and Abal M. ETV5 transcription program links BDNF and promotion of EMT at invasive front of endometrial carcinomas. Carcinogenesis 2014; 35: 2679-2686.
[123] Lunardi A, Varmeh S, Chen M, Taulli R, Guarnerio J, Ala U, Seitzer N, Ishikawa T, Carver BS, Hobbs RM, Quarantotti V, Ng C, Berger AH, Nardella C, Poliseno L, Montironi R, Castillo-Martin M, Cordon-Cardo C, Signoretti S and Pandolfi PP. Suppression of CHK1 by ETS family members promotes DNA damage response bypass and tumorigenesis. Cancer Discov 2015; 5: 550-563.
[124] Shin S, Oh S, An S and Janknecht R. ETS variant 1 regulates matrix metalloproteinase-7 transcription in LNCaP prostate cancer cells. Oncol Rep 2013; 29: 306-314.
[125] Liu CY, Yu T, Huang Y, Cui L and Hong W. ETS (E26 transformation-specific) up-regulation of the transcriptional co-activator TAZ promotes cell migration and metastasis in prostate cancer. J Biol Chem 2017; 292: 9420-9430.
[126] Qi M, Liu Z, Shen C, Wang L, Zeng J, Wang C, Li C, Fu W, Sun Y and Han B. Overexpression of ETV4 is associated with poor prognosis in prostate cancer: involvement of uPA/uPAR and MMPs. Tumour Biol 2015; 36: 3565-3572.
[127] Hollenhorst PC, Paul L, Ferris MW and Graves BJ. The ETS gene ETV4 is required for anchorage-independent growth and a cell proliferation gene expression program in PC3 prostate cells. Genes Cancer 2011; 1: 1044-1052.
[128] Hao L, Pang K, Pang H, Zhang J, Zhang Z, He H, Zhou R, Shi Z and Han C. Knockdown of P3H4 inhibits proliferation and invasion of bladder cancer. Aging (Albany NY) 2020; 12: 2156-2168.
[129] Keld R, Guo B, Downey P, Gulmann C, Ang YS and Sharrocks AD. The ERK MAP kinase-PEA3/ETV4-MMP-1 axis is operative in oesophageal adenocarcinoma. Mol Cancer 2010; 9: 313.
[130] Chen Y, Zou H, Yang LY, Li Y, Wang L, Hao Y and Yang JL. ER81-shRNA inhibits growth of triple-negative human breast cancer cell line MDA-

MB-231 in vivo and in vitro. Asian Pac J Cancer Prev 2012; 13: 2385-2392.
[131] Xiaohui C, Xin LI and Dehua WU. E26 transformation-specific variant 4 promotes sorafenib and cisplatin resistance in hepatocellular carcinoma cells in vitro. Nan Fang Yi Ke Da Xue Xue Bao 2019; 39: 875-882.
[132] Deshmukh SK, Singh AP and Singh S. ETV4: an emerging target in pancreatic cancer. Oncoscience 2018; 5: 260-261.
[133] Tyagi N, Deshmukh SK, Srivastava SK, Azim S, Ahmad A, Al-Ghadhban A, Singh AP, Carter JE, Wang B and Singh S. ETV4 facilitates cell-cycle progression in pancreatic cells through transcriptional regulation of cyclin D1. Mol Cancer Res 2018; 16: 187-196.
[134] Kim H, Datta A, Talwar S, Saleem SN, Mondal D and Abdel-Mageed AB. Estradiol-ERβ2 signaling axis confers growth and migration of CRPC cells through TMPRSS2-ETV5 gene fusion. Oncotarget 2017; 8: 62820-62833.
[135] Xiao BD, Zhao YJ, Jia XY, Wu J, Wang YG and Huang F. Multifaceted p21 in carcinogenesis, stemness of tumor and tumor therapy. World J Stem Cells 2020; 12: 481-487.
[136] Cosi I, Pellecchia A, De Lorenzo E, Torre E, Sica M, Nesi G, Notaro R and De Angioletti M. ETV4 promotes late development of prostatic intraepithelial neoplasia and cell proliferation through direct and p53-mediated downregulation of p21. J Hematol Oncol 2020; 13: 112.
[137] Ladam F, Damour I, Dumont P, Kherrouche Z, de Launoit Y, Tulasne D and Chotteau-Lelievre A. Loss of a negative feedback loop involving pea3 and cyclin d2 is required for pea3-induced migration in transformed mammary epithelial cells. Mol Cancer Res 2013; 11: 1412-1424.
[138] Jiang J, Wei Y, Liu D, Zhou J, Shen J, Chen X, Zhang S, Kong X and Gu J. E1AF promotes breast cancer cell cycle progression via upregulation of Cyclin D3 transcription. Biochem Biophys Res Commun 2007; 358: 53-58.
[139] Zhang Y, Gu ML, Zhou XX, Ma H, Yao HP and Ji F. Altered expression of ETV1 and its contribution to tumorigenic phenotypes in gastrointestinal stromal tumors. Oncol Rep 2014; 32: 927-934.
[140] Yang L, Shi P, Zhao G, Xu J, Peng W, Zhang J, Zhang G, Wang X, Dong Z, Chen F and Cui H. Targeting cancer stem cell pathways for cancer therapy. Signal Transduct Target Ther 2020; 5: 8.
[141] Chivu-Economescu M, Necula LG, Matei L, Dragu DL, Neagu AI, Alexiu I, Bleotu C and Diaconu CC. Gastrointestinal cancer stem cells as targets for innovative immunotherapy. World J Gastroenterol 2020; 26: 1580-1593.
[142] Ahmad ST, Rogers AD, Chen MJ, Dixit R, Adnani L, Frankiw LS, Lawn SO, Blough MD, Alshehri M, Wu W, Marra MA, Robbins SM, Cairncross JG, Schuurmans C and Chan JA. Capicua regulates neural stem cell proliferation and lineage specification through control of Ets factors. Nat Commun 2019; 10: 2000.
[143] Menendez ST, Rey V, Martinez-Cruzado L, Gonzalez MV, Morales-Molina A, Santos L, Blanco V, Alvarez C, Estupiñan O, Allonca E, Rodrigo JP, García-Castro J, Garcia-Pedrero JM and Rodriguez R. SOX2 expression and transcriptional activity identifies a subpopulation of cancer stem cells in sarcoma with prognostic implications. Cancers (Basel) 2020; 12: 964.
[144] Siddiqui Z, Srivastava AN, Sankhwar SN, Dalela D, Singh V, Zaidi N, Fatima N, Bano I and Anjum S. Synergic effects of cancer stem cells markers, CD44 and embryonic stem cell transcription factor Nanog, on bladder cancer prognosis. Br J Biomed Sci 2020; 77: 69-75.
[145] Park SW, Do HJ, Choi W, Song H, Chung HJ and Kim JH. NANOG gene expression is regulated by the ETS transcription factor ETV4 in human embryonic carcinoma NCCIT cells. Biochem Biophys Res Commun 2017; 487: 532-538.
[146] Watanabe H, Ma Q, Peng S, Adelmant G, Swain D, Song W, Fox C, Francis JM, Pedamallu CS, DeLuca DS, Brooks AN, Wang S, Que J, Rustgi AK, Wong KK, Ligon KL, Liu XS, Marto JA, Meyerson M and Bass AJ. SOX2 and p63 colocalize at genetic loci in squamous cell carcinomas. J Clin Invest 2014; 124: 1636-1645.
[147] Liao S, Davoli T, Leng Y, Li MZ, Xu Q and Elledge SJ. A genetic interaction analysis identifies cancer drivers that modify EGFR dependency. Genes Dev 2017; 31: 184-196.
[148] Park SM, Hwang CY, Cho SH, Lee D, Gong JR, Lee S, Nam S and Cho KH. Systems analysis identifies potential target genes to overcome cetuximab resistance in colorectal cancer cells. FEBS J 2019; 286: 1305-1318.
[149] Uitdehaag JCM, Kooijman JJ, de Roos J, Prinsen MBW, Dylus J, Willemsen-Seegers N, Kawase Y, Sawa M, de Man J, van Gerwen SJC, Buijsman RC and Zaman GJR. Combined cellular and biochemical profiling to identify predictive drug response biomarkers for kinase inhibitors approved for clinical use between 2013 and 2017. Mol Cancer Ther 2019; 18: 470-481.
[150] Gupta A, Towers C, Willenbrock F, Brant R, Hodgson DR, Sharpe A, Smith P, Cutts A, Schuh A, Asher R, Myers K, Love S, Collins L, Wise A, Middleton MR and Macaulay VM. Dual-specificity protein phosphatase DUSP4 regulates response to MEK inhibition in BRAF wild-type melanoma. Br J Cancer 2020; 122: 506-516.
[151] Kacew AJ, Harris EJ, Lorch JH, Haddad RI, Chau NG, Rabinowits G, LeBoeuf NR, Schmults CD, Thakuria M, MacConaill LE and Hanna GJ. Chromosome 3q arm gain linked to immuno-

therapy response in advanced cutaneous squamous cell carcinoma. Eur J Cancer 2019; 113: 1-9.
[152] Li Z, Wang B, Gu S, Jiang P, Sahu A, Chen CH, Han T, Shi S, Wang X, Traugh N, Liu H, Liu Y, Wu Q, Brown M, Xiao T, Boland GM and Shirley Liu X. CRISPR screens identify essential cell growth mediators in BRAF inhibitor-resistant melanoma. Genomics Proteomics Bioinformatics 2020; 18: 26-40.
[153] Zhao Y, Liu J, Hong Q, Yang C, Chen L, Chen Y, Wang Q, Zhao K and Jin W. Involvement of MyoD and PEA3 in regulation of transcription activity of MDR1 gene. Acta Biochim Biophys Sin (Shanghai) 2010; 42: 900-907.
[154] Hu J, Zhu W, Wei B, Wen H, Mao S, Xu H, Hu M, Yang T and Jiang H. Antitumoral action of icaritin in LNCaP prostate cancer cells by regulating PEA3/HER2/AR signaling. Anticancer Drugs 2016; 27: 944-952.
[155] Xing X, Wang SC, Xia W, Zou Y, Shao R, Kwong KY, Yu Z, Zhang S, Miller S, Huang L and Hung MC. The ets protein PEA3 suppresses HER-2/neu overexpression and inhibits tumorigenesis. Nat Med 2000; 6: 189-195.
[156] Span PN, Manders P, Heuvel JJ, Beex LV and Sweep CG. E1AF expression levels are not associated with prognosis in human breast cancer. Breast Cancer Res Treat 2003; 79: 129-131.
[157] Iwasaki M, Nishikawa A, Akutagawa N, Fujimoto T, Teramoto M, Sakaguchi Y, Kato H, Ito M, Yoshida K and Kudo R. E1AF/PEA3 reduces the invasiveness of SiHa cervical cancer cells by activating serine proteinase inhibitor squamous cell carcinoma antigen. Exp Cell Res 2004; 299: 525-532.
[158] Liu D, Wei Y, Zhou F, Ge Y, Xu J, Chen H, Zhang W, Yun X and Jiang J. E1AF promotes mithramycin A-induced Huh-7 cell apoptosis depending on its DNA-binding domain. Arch Biochem Biophys 2008; 477: 20-26.
[159] Segalés L, Juanpere N, Lorenzo M, Albero-González R, Fumadó L, Cecchini L, Bellmunt J, Lloreta-Trull J and Hernández-Llodrà S. Strong cytoplasmic ETV1 expression has a negative impact on prostate cancer outcome. Virchows Arch 2019; 475: 457-466.
[160] Eskandari E, Mahjoubi F and Motalebzadeh J. An integrated study on TFs and miRNAs in colorectal cancer metastasis and evaluation of three co-regulated candidate genes as prognostic markers. Gene 2018; 679: 150-159.
[161] Liu HY, Zhou B, Wang L, Li Y, Zhou ZG, Sun XF, Xu B, Zeng YJ, Song JM, Luo HZ and Yang L. Association of E1AF mRNA expression with tumor progression and matrilysin in human rectal cancer. Oncology 2007; 73: 384-388.
[162] Wan G, Gao F, Chen J, Li Y, Geng M, Sun L, Liu Y, Liu H, Yang X, Wang R, Feng Y and Wang X. Nomogram prediction of individual prognosis of patients with hepatocellular carcinoma. BMC Cancer 2017; 17: 91.
[163] Chotteau-Lelièvre A, Révillion F, Lhotellier V, Hornez L, Desbiens X, Cabaret V, de Launoit Y and Peyrat JP. Prognostic value of ERM gene expression in human primary breast cancers. Clin Cancer Res 2004; 10: 7297-7303.
[164] Yuan ZY, Dai T, Wang SS, Peng RJ, Li XH, Qin T, Song LB and Wang X. Overexpression of ETV4 protein in triple-negative breast cancer is associated with a higher risk of distant metastasis. Onco Targets Ther 2014; 7: 1733-1742.
[165] Yamamoto H, Horiuchi S, Adachi Y, Taniguchi H, Nosho K, Min Y and Imai K. Expression of ets-related transcriptional factor E1AF is associated with tumor progression and over-expression of matrilysin in human gastric cancer. Carcinogenesis 2004; 25: 325-332.
[166] Hida K, Shindoh M, Yoshida K, Kudoh A, Furaoka K, Kohgo T, Fujinaga K and Totsuka Y. Expression of E1AF, an ets-family transcription factor, is correlated with the invasive phenotype of oral squamous cell carcinoma. Oral Oncol 1997; 33: 426-430.
[167] Hung YP, Fletcher CD and Hornick JL. Evaluation of ETV4 and WT1 expression in CIC-rearranged sarcomas and histologic mimics. Mod Pathol 2016; 29: 1324-1334.
[168] Smith SC, Palanisamy N, Martin E, Almenara J, McHugh JB, Choi EK, Lucas DR, Betz BL, Thomas D and Patel RM. The utility of ETV1, ETV4 and ETV5 RNA in-situ hybridization in the diagnosis of CIC-DUX sarcomas. Histopathology 2017; 70: 657-663.
[169] Kao YC, Sung YS, Chen CL, Zhang L, Dickson BC, Swanson D, Vaiyapuri S, Latif F, Alholle A, Huang SC, Hornick JL and Antonescu CR. ETV transcriptional upregulation is more reliable than RNA sequencing algorithms and FISH in diagnosing round cell sarcomas with CIC gene rearrangements. Genes Chromosomes Cancer 2017; 56: 501-510.
[170] Le Guellec S, Velasco V, Pérot G, Watson S, Tirode F and Coindre JM. ETV4 is a useful marker for the diagnosis of CIC-rearranged undifferentiated round-cell sarcomas: a study of 127 cases including mimicking lesions. Mod Pathol 2016; 29: 1523-1531.
[171] Tu JJ, Rohan S, Kao J, Kitabayashi N, Mathew S and Chen YT. Gene fusions between TMPRSS2 and ETS family genes in prostate cancer: frequency and transcript variant analysis by RT-PCR and FISH on paraffin-embedded tissues. Mod Pathol 2007; 20: 921-928.
[172] Urano F, Umezawa A, Yabe H, Hong W, Yoshida K, Fujinaga K and Hata J. Molecular analysis of Ewing's sarcoma: another fusion gene, EWS-E1AF, available for diagnosis. Jpn J Cancer Res 1998; 89: 703-711.

[173] Hsing M, Wang Y, Rennie PS, Cox ME and Cherkasov A. ETS transcription factors as emerging drug targets in cancer. Med Res Rev 2020; 40: 413-430.
[174] Rahim S, Beauchamp EM, Kong Y, Brown ML, Toretsky JA and Üren A. YK-4-279 inhibits ERG and ETV1 mediated prostate cancer cell invasion. PLoS One 2011; 6: e19343.
[175] Rahim S, Minas T, Hong SH, Justvig S, Çelik H, Kont YS, Han J, Kallarakal AT, Kong Y, Rudek MA, Brown ML, Kallakury B, Toretsky JA and Üren A. A small molecule inhibitor of ETV1, YK-4-279, prevents prostate cancer growth and metastasis in a mouse xenograft model. PLoS One 2014; 9: e114260.
[176] Yu L, Wu X, Chen M, Huang H, He Y, Wang H, Li D, Du Z, Zhang K, Goodin S and Zheng X. The effects and mechanism of YK-4-279 in combination with docetaxel on prostate cancer. Int J Med Sci 2017; 14: 356-366.
[177] Pop MS, Stransky N, Garvie CW, Theurillat JP, Hartman EC, Lewis TA, Zhong C, Culyba EK, Lin F, Daniels DS, Pagliarini R, Ronco L, Koehler AN and Garraway LA. A small molecule that binds and inhibits the ETV1 transcription factor oncoprotein. Mol Cancer Ther 2014; 13: 1492-1502.
[178] Kollareddy M, Sherrard A, Park JH, Szemes M, Gallacher K, Melegh Z, Oltean S, Michaelis M, Cinatl J Jr, Kaidi A and Malik K. The small molecule inhibitor YK-4-279 disrupts mitotic progression of neuroblastoma cells, overcomes drug resistance and synergizes with inhibitors of mitosis. Cancer Lett 2017; 403: 74-85.
[179] Euhus D, Bu D, Xie XJ, Sarode V, Ashfaq R, Hunt K, Xia W, O'Shaughnessy J, Grant M, Arun B, Dooley W, Miller A, Flockhart D and Lewis C. Tamoxifen downregulates ets oncogene family members ETV4 and ETV5 in benign breast tissue: implications for durable risk reduction. Cancer Prev Res (Phila) 2011; 4: 1852-1862.
[180] Yen CC, Chen LT, Li CF, Chen SC, Chua WY, Lin YC, Yen CH, Chen YC, Yang MH, Chao Y and Fletcher JA. Identification of phenothiazine as an ETV1-targeting agent in gastrointestinal stromal tumors using the connectivity map. Int J Oncol 2019; 55: 536-546.
[181] Nath AI and Nair AS. Fingerprint-based similarity search identified p-anisidine as an anticancer agent in HeLa and a prospective phytochemical ETV1 transcription factor inhibitor. J Biomol Struct Dyn 2020; 1-8.
[182] Cooper CD, Newman JA, Aitkenhead H, Allerston CK and Gileadi O. Structures of the ets protein DNA-binding domains of transcription factors Etv1, Etv4, Etv5, and Fev: determinants of DNA binding and redox regulation by disulfide bond formation. J Biol Chem 2015; 290: 13692-13709.
[183] Orlando G, Law PJ, Cornish AJ, Dobbins SE, Chubb D, Broderick P, Litchfield K, Hariri F, Pastinen T, Osborne CS, Taipale J and Houlston RS. Promoter capture Hi-C-based identification of recurrent noncoding mutations in colorectal cancer. Nat Genet 2018; 50: 1375-1380.
[184] Currie SL, Doane JJ, Evans KS, Bhachech N, Madison BJ, Lau DKW, McIntosh LP, Skalicky JJ, Clark KA and Graves BJ. ETV4 and AP1 transcription factors form multivalent interactions with three sites on the MED25 activator-interacting domain. J Mol Biol 2017; 429: 2975-2995.

Table S1. PEA3 subfamily regulates the expression of genes associated with cell migration and invasion

Cancer type	PEA3 member	Gene	Finding	Reference
Bladder cancer	ETV4	P3H4	ETV4 binds directly to the promoter region of P3H4 and activates its transcription, prompting cancer proliferation and invasion.	[1]
Bladder cancer	ETV5	TAZ	ETV5 is involved in cancer invasion and metastasis by upregulating TAZ expression and activating Hippo pathway.	[2]
Breast cancer	ETV1	hTERT	HER2 interacts with ETV1 to synergistically activate hTERT transcription, conferring the aggressive biologic behavior in breast cancer.	[3]
Breast cancer	ETV5	hTERT	ETV5 and c-Myc synergistically mediate hTERT activation via composite Ets/E-box motifs.	[4]
Breast cancer	ETV1	Rcl	ETV1 and HER2/Neu coordinate to upregulate the Rcl expression. ETV1 binds to the Rcl promoter and increases tumor grade.	[5]
Breast cancer	ETV1	Smad7	HER2/Neu collaborates with ETV1 to activate Smad7 transcription.	[6]
Breast cancer	ETV4	MMP13	ETV4 promotes cancer proliferation, migration, invasion, and anchorage-independent growth by targeting its target gene MMP13.	[7]
Breast cancer (ER-negative)	ETV4	MMP1, CXCR4	ETV4 could promote cancer progression and metastasis by activating its well-characterized target genes CXCR4 and MMP1.	[8]
Chondrosarcoma	ETV5	MMP2	ETV5 upregulates MMP2 expression and promotes chondrosarcoma metastasis.	[9]
ccRCC	ETV4	FOSL1	ETV4 promotes ccRCC metastasis by activating the pro-metastatic gene FOSL1 in a PI3K-AKT dependent manner.	[10]
Colorectal cancer	ETV4	MMP7, MMP14	ETV4 acts as a mediator of cancer metastasis by regulating MMP7 and MMP14 expression.	[11]
Colorectal cancer	ETV4	COX2, MMP7	ETV4 activates transcriptional activity of COX-2 and MMP-7, leading to cancer progression.	[12]
Colorectal cancer	ETV4	MMP1, MMP7, COX2, iNOS	ETV4 expression is positively correlated with the expression of MMP1, MMP7, COX2, and iNOS, ETV4-MMP1-MMP-7-COX-2-iNOS axis contributes to colorectal cancer progression.	[13, 14]
Colorectal cancer	ETV5	PDGF-BB	ETV5 directly binds to the promoter region of PDGF-BB, which mediates colorectal cancer angiogenesis.	[15]
Endometrial cancer	ETV4	ER	ETV4 is a candidate factor regulating ER in endometrial cancer cells. The high level of ER contributes to cancer progression.	[16]
Endometrial cancer	ETV5	MMP2	ETV5 regulates MMP2 expression to confer tumor invasion ability.	[17]
Endometrial cancer	ETV5	NID1, NUPR1	ETV5 promotes cancer migration and invasion by directly upregulating NID1 and NUPR1 transcriptional activity in vitro and in vivo.	[18]
Gastric cancer	ETV4	KDM5D*	ETV4 might promote gastric cancer cell metastasis by negatively modulating KDM5D.	[19]
Gastric cancer	ETV4	KIF2A	ETV4 directly upregulates the expression of KIF2 to promote cell migration and invasion.	[20]

Gastric cancer	ETV4	ME1	ETV4 directly binds to ME1 promoter to promote cancer metastasis.	[21]
Glioma	ETV4	GalT V	ETV4 physically interacts with Sp1 transcription factor and forms an ETV4/Sp1 complex, the ETV4/Sp1 complex binds to the GalT V promoter, inducing glioma invasion.	[22]
Hepatocellular carcinoma	ETV4	uPAR	PBK promotes migration invasion by enhancing the binding of ETV4 to the uPAR promoter.	[23]
Hepatocellular carcinoma	ETV4	MMP1	CIC deficiency increases the expression of its downstream target ETV4, which further upregulates MMP1 expression and promotes hepatocellular carcinoma progression.	[24]
Lung adenocarcinoma	ETV4	MSI2	ETV4 increases MSI2 expression by directly binding to the promoter of MSI2, which promotes the proliferation and invasion of lung adenocarcinoma.	[25]
Lung cancer	ETV1/4/5	MMP2	ETV1/ETV4/ETV5 overexpression upregulates MMP2 target gene, which leads to the migration and invasion of lung cancer cells.	[26]
Lung cancer (NSCLC)	ETV4	PXN, MMP1	ETV4 overexpression promotes cancer progression by upregulating PXN and MMP1 transcriptionally.	[27]
Lung cancer (NSCLC)	ETV4	Rho	ETV4 activates the Rho protein in an HGF-enhanced manner, which further increases the phosphorylation of MLC and induces the malignancy potential of NSCLC cells.	[28]
Melanoma	ETV4	MMP25	ETV4 induces MMP25 overexpression and leads to melanoma metastasis.	[29]
Neuroblastoma	ETV5	RET	ETV5 promotes RET gene transcription by binding to the RET promoter, which drives neuroblastoma oncogenesis.	[30]
Oesophageal adenocarcinoma	ETV4	MMP1	ETV4 promotes cancer proliferation and invasive by targeting MMP1.	[31]
Oesophageal squamous cell carcinoma	ETV4	MMP2, MMP9	ETV4 induces cancer metastasis by enhancing MMP-2 and MMP-9 expression.	[32]
Oral squamous cell carcinoma	ETV4	MMP1/3/9	HGF induces the expression of ETV4, which in turn activates MMP1/3/9 and leads to oral cancer cell invasion.	[33]
Ovarian cancer	ETV5	FOXM1	ETV5 upregulates FOXM1 expression by binding to the proximal promoter region of FOXM1, which promotes cancer progression.	[34]
Pancreatic cancer	ETV1	Sparc, Has2	By regulating two novel downstream factors Sparc and Has2, ETV1 increases the invasive capacity of pancreatic cancer cells.	[35]
Prostate cancer	ETV1	β-catenin	ETV1 could stabilize β-catenin, which leads to the increased accumulation of β-catenin within prostate cancer cells, promoting malignant transformation in cancer.	[36]
Prostate cancer	ETV1	MMP1, MMP7	ETV1 activates transcription of its target genes MMP-1 and MMP-7, which regulates cell migration and invasion.	[37, 38]

Prostate cancer	ETV1	CHK1*	ETV1 contributes to DNA damage accumulation, genetic instability, and prostate tumor progression by directly repressing the expression of CHK1.	[39]
Prostate cancer	ETV4	uPA, MMP2, MMP9	ETV4 regulates uPA expression by directly binding to the uPA promoter region. Besides, uPA binds to its receptor uPAR, activating MMP2 and MMP9 expression and inducing tumor metastasis.	[40]
Prostate cancer	ETV4	MYC	ETV4 directly binds to the 5' and 3' MYC enhancers and regulates MYC expression to increase cellular motility.	[41]
Prostate cancer	ETV4	TAZ	ETV4 directly binds to the TAZ promoter region. TAZ upregulates its target gene SH3BP1, which promots cell migration and anchorage-independent growth.	[42]
Thyroid cancer	ETV1/4/5	TERT	ETV5 directly binds to the TERT promoter in a mutation-dependent manner, which increases the invasiveness of thyroid carcinoma.	[43, 44]
Thyroid cancer	ETV5	PIK3A	ETV5 promotes cell growth and migration by targeting and activating PIK3CA transcriptionally.	[45]

ER, estrogen receptor; MMP, matrix metalloproteinase; ccRCC, Clear cell renal cell carcinoma; PDGF-BB, platelet-derived growth factor BB; NID1, Nidogen 1; NUPR1, Nuclear Protein 1; MLC, myosin light chain; NSCLC, non-small-cell lung cancer; CHK1, Checkpoint kinase 1. *Genes downregulated by PEA3 subfamily.

References

[1] Hao L, Pang K, Pang H, Zhang J, Zhang Z, He H, Zhou R, Shi Z and Han C. Knockdown of P3H4 inhibits proliferation and invasion of bladder cancer. Aging (Albany NY) 2020; 12: 2156-2168.

[2] di Martino E, Alder O, Hurst CD and Knowles MA. ETV5 links the FGFR3 and Hippo signalling pathways in bladder cancer. Sci Rep 2019; 9: 5740.

[3] Vageli D, Ioannou MG and Koukoulis GK. Transcriptional activation of hTERT in breast carcinomas by the Her2-ER81-related pathway. Oncol Res 2009; 17: 413-423.

[4] Zhang F, Wang S and Zhu J. ETS variant transcription factor 5 and c-Myc cooperate in derepressing the human telomerase gene promoter via composite ETS/E-box motifs. J Biol Chem 2020; 295: 10062-10075.

[5] Shin S, Bosc DG, Ingle JN, Spelsberg TC and Janknecht R. Rcl is a novel ETV1/ER81 target gene upregulated in breast tumors. J Cell Biochem 2008; 105: 866-874.

[6] Dowdy SC, Mariani A and Janknecht R. HER2/Neu- and TAK1-mediated up-regulation of the transforming growth factor beta inhibitor Smad7 via the ETS protein ER81. J Biol Chem 2003; 278: 44377-44384.

[7] Dumortier M, Ladam F, Damour I, Vacher S, Bièche I, Marchand N, de Launoit Y, Tulasne D and Chotteau-Lelièvre A. ETV4 transcription factor and MMP13 metalloprotease are interplaying actors of breast tumorigenesis. Breast Cancer Res 2018; 20: 73.

[8] Kim HJ, Kim SH, Yu EJ, Seo WY and Kim JH. A positive role of DBC1 in PEA3-mediated progression of estrogen receptor-negative breast cancer. Oncogene 2015; 34: 4500-4508.

[9] Power PF, Mak IW, Singh S, Popovic S, Gladdy R and Ghert M. ETV5 as a regulator of matrix metalloproteinase 2 in human chondrosarcoma. J Orthop Res 2013; 31: 493-501.

[10] Xu L, Hu H, Zheng LS, Wang MY, Mei Y, Peng LX, Qiang YY, Li CZ, Meng DF, Wang MD, Liu ZJ, Li XJ, Huang BJ and Qian CN. ETV4 is a theranostic target in clear cell renal cell carcinoma that promotes metastasis by activating the pro-metastatic gene FOSL1 in a PI3K-AKT dependent manner. Cancer Lett 2020; 482: 74-89.

[11] Mesci A, Taeb S, Huang X, Jairath R, Sivaloganathan D and Liu SK. Pea3 expression promotes the invasive and metastatic potential of colorectal carcinoma. World J Gastroenterol 2014; 20: 17376-17387.

[12] Boedefeld WM 2nd, Soong R, Weiss H, Diasio RB, Urist MM, Bland KI and Heslin MJ. E1A-F is overexpressed early in human colorectal neoplasia and associated with cyclooxygenase-2 and matrix metalloproteinase-7. Mol Carcinog 2005; 43: 13-17.

[13] Nosho K, Yoshida M, Yamamoto H, Taniguchi H, Adachi Y, Mikami M, Hinoda Y and Imai K. Association of Ets-related transcriptional factor E1AF expression with overexpression of matrix metalloproteinases, COX-2 and iNOS in the early stage of colorectal carcinogenesis. Carcinogenesis 2005; 26: 892-899.

[14] Horiuchi S, Yamamoto H, Min Y, Adachi Y, Itoh F and Imai K. Association of ets-related transcriptional factor E1AF expression with tumour progression and overexpression of MMP-1 and matrilysin in human colorectal cancer. J Pathol 2003; 200: 568-576.

[15] Cheng X, Jin Z, Ji X, Shen X, Feng H, Morgenlander W, Ou B, Wu H, Gao H, Ye F, Zhang Y, Peng Y, Liang J, Jiang Y, Zhang T, Qiu W, Lu X and Zhao R. ETS variant 5 promotes colorectal cancer angiogenesis by targeting platelet-derived growth factor BB. Int J Cancer 2019; 145: 179-191.

[16] Rodriguez AC, Vahrenkamp JM, Berrett KC, Clark KA, Guillen KP, Scherer SD, Yang CH, Welm BE, Janát-Amsbury MM, Graves BJ and Gertz J. ETV4 is necessary for estrogen signaling and growth in endometrial cancer cells. Cancer Res 2020; 80: 1234-1245.

[17] Monge M, Colas E, Doll A, Gonzalez M, Gil-Moreno A, Planaguma J, Quiles M, Arbos MA, Garcia A, Castellvi J, Llaurado M, Rigau M, Alazzouzi H, Xercavins J, Alameda F, Reventos J and Abal M. ERM/ETV5 up-regulation plays a role during myometrial infiltration through matrix metalloproteinase-2 activation in endometrial cancer. Cancer Res 2007; 67: 6753-6759.

[18] Pedrola N, Devis L, Llauradó M, Campoy I, Martinez-Garcia E, Garcia M, Muinelo-Romay L, Alonso-Alconada L, Abal M, Alameda F, Mancebo G, Carreras R, Castellví J, Cabrera S, Gil-Moreno A, Matias-Guiu X, Iovanna JL, Colas E, Reventós J and Ruiz A. Nidogen 1 and nuclear protein 1: novel targets of ETV5 transcription factor involved in endometrial cancer invasion. Clin Exp Metastasis 2015; 32: 467-478.

[19] Cai LS, Chen QX, Fang SY, Lian MQ, Lian MJ and Cai MZ. ETV4 promotes the progression of gastric cancer through regulating KDM5D. Eur Rev Med Pharmacol Sci 2020; 24: 2442-2451.

[20] Zhang X, Wang Y, Liu X, Zhao A, Yang Z, Kong F, Sun L, Yu Y and Jiang L. KIF2A promotes the progression via AKT signaling pathway and is upregulated by transcription factor ETV4 in human gastric cancer. Biomed Pharmacother 2020; 125: 109840.

[21] Lu YX, Ju HQ, Liu ZX, Chen DL, Wang Y, Zhao Q, Wu QN, Zeng ZL, Qiu HB, Hu PS, Wang ZQ, Zhang DS, Wang F and Xu RH. ME1 regulates nadph homeostasis to promote gastric cancer growth and metastasis. Cancer Res 2018; 78: 1972-1985.

[22] Jiang J, Wei Y, Shen J, Liu D, Chen X, Zhou J, Zong H, Yun X, Kong X, Zhang S, Yang Y and Gu J. Functional interaction of E1AF and Sp1 in glioma invasion. Mol Cell Biol 2007; 27: 8770-8782.

[23] Yang QX, Zhong S, He L, Jia XJ, Tang H, Cheng ST, Ren JH, Yu HB, Zhou L, Zhou HZ, Ren F, Hu ZW, Gong R, Huang AL and Chen J. PBK overexpression promotes metastasis of hepatocellular carcinoma via activating ETV4-uPAR signaling pathway. Cancer Lett 2019; 452: 90-102.
[24] Kim E, Kim D, Lee JS, Yoe J, Park J, Kim CJ, Jeong D, Kim S and Lee Y. Capicua suppresses hepatocellular carcinoma progression by controlling the ETV4-MMP1 axis. Hepatology 2018; 67: 2287-2301.
[25] Cheng T, Zhang Z, Cheng Y, Zhang J, Tang J, Tan Z, Liang Z, Chen T, Liu Z, Li J, Zhao J and Zhou R. ETV4 promotes proliferation and invasion of lung adenocarcinoma by transcriptionally upregulating MSI2. Biochem Biophys Res Commun 2019; 516: 278-284.
[26] Kherrouche Z, Monte D, Werkmeister E, Stoven L, De Launoit Y, Cortot AB, Tulasne D and Chotteau-Lelievre A. PEA3 transcription factors are downstream effectors of Met signaling involved in migration and invasiveness of Met-addicted tumor cells. Mol Oncol 2015; 9: 1852-1867.
[27] Wang Y, Ding X, Liu B, Li M, Chang Y, Shen H, Xie SM, Xing L and Li Y. ETV4 overexpression promotes progression of non-small cell lung cancer by upregulating PXN and MMP1 transcriptionally. Mol Carcinog 2020; 59: 73-86.
[28] Hakuma N, Kinoshita I, Shimizu Y, Yamazaki K, Yoshida K, Nishimura M and Dosaka-Akita H. E1AF/PEA3 activates the Rho/Rho-associated kinase pathway to increase the malignancy potential of non-small-cell lung cancer cells. Cancer Res 2005; 65: 10776-10782.
[29] Chen Y, Sumardika IW, Tomonobu N, Winarsa Ruma IM, Kinoshita R, Kondo E, Inoue Y, Sato H, Yamauchi A, Murata H, Yamamoto KI, Tomida S, Shien K, Yamamoto H, Soh J, Liu M, Futami J, Sasai K, Katayama H, Kubo M, Putranto EW, Hibino T, Sun B, Nishibori M, Toyooka S and Sakaguchi M. Melanoma cell adhesion molecule is the driving force behind the dissemination of melanoma upon S100A8/A9 binding in the original skin lesion. Cancer Lett 2019; 452: 178-190.
[30] Lopez-Delisle L, Pierre-Eugène C, Louis-Brennetot C, Surdez D, Raynal V, Baulande S, Boeva V, Grossetête-Lalami S, Combaret V, Peuchmaur M, Delattre O and Janoueix-Lerosey I. Activated ALK signals through the ERK-ETV5-RET pathway to drive neuroblastoma oncogenesis. Oncogene 2018; 37: 1417-1429.
[31] Keld R, Guo B, Downey P, Gulmann C, Ang YS and Sharrocks AD. The ERK MAP kinase-PEA3/ETV4-MMP-1 axis is operative in oesophageal adenocarcinoma. Mol Cancer 2010; 9: 313.
[32] Fung TM, Ng KY, Tong M, Chen JN, Chai S, Chan KT, Law S, Lee NP, Choi MY, Li B, Cheung AL, Tsao SW, Qin YR, Guan XY, Chan KW and Ma S. Neuropilin-2 promotes tumourigenicity and metastasis in oesophageal squamous cell carcinoma through ERK-MAPK-ETV4-MMP-E-cadherin deregulation. J Pathol 2016; 239: 309-319.
[33] Hanzawa M, Shindoh M, Higashino F, Yasuda M, Inoue N, Hida K, Ono M, Kohgo T, Nakamura M, Notani K, Fukuda H, Totsuka Y, Yoshida K and Fujinaga K. Hepatocyte growth factor upregulates E1AF that induces oral squamous cell carcinoma cell invasion by activating matrix metalloproteinase genes. Carcinogenesis 2000; 21: 1079-1085.
[34] Llauradó M, Majem B, Castellví J, Cabrera S, Gil-Moreno A, Reventós J and Ruiz A. Analysis of gene expression regulated by the ETV5 transcription factor in OV90 ovarian cancer cells identifies FOXM1 overexpression in ovarian cancer. Mol Cancer Res 2012; 10: 914-924.
[35] Heeg S, Das KK, Reichert M, Bakir B, Takano S, Caspers J, Aiello NM, Wu K, Neesse A, Maitra A, Iacobuzio-Donahue CA, Hicks P and Rustgi AK. ETS-transcription factor ETV1 regulates stromal expansion and metastasis in pancreatic cancer. Gastroenterology 2016; 151: 540-553, e514.
[36] Morsalin S, Yang C, Fang J, Reddy S, Kayarthodi S, Childs E, Matthews R, Rao VN and Reddy ESP. Molecular mechanism of β-Catenin signaling pathway inactivation in ETV1-positive prostate cancers. J Pharm Sci Pharmacol 2015; 2: 208-216.
[37] Oh S, Shin S, Lightfoot SA and Janknecht R. 14-3-3 proteins modulate the ETS transcription factor ETV1 in prostate cancer. Cancer Res 2013; 73: 5110-5119.
[38] Shin S, Oh S, An S and Janknecht R. ETS variant 1 regulates matrix metalloproteinase-7 transcription in LNCaP prostate cancer cells. Oncol Rep 2013; 29: 306-314.
[39] Lunardi A, Varmeh S, Chen M, Taulli R, Guarnerio J, Ala U, Seitzer N, Ishikawa T, Carver BS, Hobbs RM, Quarantotti V, Ng C, Berger AH, Nardella C, Poliseno L, Montironi R, Castillo-Martin M, Cordon-Cardo C, Signoretti S and Pandolfi PP. Suppression of CHK1 by ETS family members promotes DNA damage response bypass and tumorigenesis. Cancer Discov 2015; 5: 550-563.
[40] Qi M, Liu Z, Shen C, Wang L, Zeng J, Wang C, Li C, Fu W, Sun Y and Han B. Overexpression of ETV4 is associated with poor prognosis in prostate cancer: involvement of uPA/uPAR and MMPs. Tumour Biol 2015; 36: 3565-3572.
[41] Hollenhorst PC, Paul L, Ferris MW and Graves BJ. The ETS gene ETV4 is required for anchorage-independent growth and a cell proliferation gene expression program in PC3 prostate cells. Genes Cancer 2011; 1: 1044-1052.
[42] Liu CY, Yu T, Huang Y, Cui L and Hong W. ETS (E26 transformation-specific) up-regulation of the transcriptional co-activator TAZ promotes cell migration and metastasis in prostate cancer. J Biol Chem 2017; 292: 9420-9430.

[43] Song YS, Yoo SK, Kim HH, Jung G, Oh AR, Cha JY, Kim SJ, Cho SW, Lee KE, Seo JS and Park YJ. Interaction of BRAF-induced ETS factors with mutant TERT promoter in papillary thyroid cancer. Endocr Relat Cancer 2019; 26: 629-641.
[44] Bullock M, Lim G, Zhu Y, Åberg H, Kurdyukov S and Clifton-Bligh R. ETS Factor ETV5 activates the mutant telomerase reverse transcriptase promoter in thyroid cancer. Thyroid 2019; 29: 1623-1633.
[45] Meng D, Li Z, Ma X, Wu L, Fu L and Qin G. ETV5 overexpression contributes to tumor growth and progression of thyroid cancer through PIK3CA. Life Sci 2020; 253: 117693.

Table S2. miRNAs and drugs targeting PEA3 subfamily

Cancer type	PEA3 member	miRNA/drug	Patient samples	In-vitro model	Functions
Prostate cancer	ETV1	miR-129-5p	30 tumor tissues and matched adjacent normal tissues	RWPE-1, PC-3, DU145, and LNCaP	Through the repression of ETV1 expression, miR-129-5p could inactivate YAP signaling and inhibit cell proliferation.
Lung adenocarcinoma	ETV1	miR-1224-3p	52 tumor tissues and matched adjacent normal tissues	HBE, HCC827, NCI-H23, SPC-A1, H1975, H1299, and A549	Circ-ZNF609 enhances lung adenocarcinoma progression by increasing oncogenic EVT1 expression via sponging miR-1224-3p.
Glioma	ETV1	miR-195-5p	/	hCMEC/D3, HEK293T, U87, NHAs	miR-195-5p directly targets ETV1 3'-UTR and reduces its expression.
Lung cancer	ETV1	miR-582-5p	Blood samples of 38 lung cancer and 23 healthy controls	/	ETV1 is regulated by miR-582-5p in lung cancer.
Triple-negative breast cancer	ETV1	miR-17-5p	105 tumor tissues and matched adjacent normal tissues	MCF 10A, MDA-MB-231, BT-549, Hs578 T	miR-17-5p suppresses cell proliferation and invasion by directly targeting ETV1.
Gastrointestinal stromal tumors	ETV1	miR-17/20a	50 primary GIST tissues and10 GI-LMS tissues	GIST-T1, GIST-882	Overexpression of miR-17 and miR-20a affects the cell cycle and induces apoptosis by targeting ETV1 in GIST cells.
Glioblastoma	ETV5	miR-8067	3 tumor tissues and matched adjacent normal tissues	/	Low expression of ETV5, regulated by miR-8067, is significantly associated with a good prognosis.
Melanoma	ETV1	miR 17	/	WM-266-4, 624mel	miR-17 enhances the migration of melanoma cells by downregulating its target gene ETV1.
Prostate cancer	ETV1	YK-4-279	/	LNCaP, PC3	YK-4-279 inhibits ETV1 biological activity in fusion-positive prostate cancer cells, leading to decreased motility and invasion.
Melanoma and prostate cancer	ETV1	BRD32048	/	501mel, SK-MEL-28, LNCaP, PC3	BRD32048 binds to ETV1 directly, modulating the transcriptional activity of ETV1.
Breast cancer	ETV4, ETV5	Tamoxifen	69 women at increased risk for breast cancer (37 received tamoxifen and 32 received placebo)	/	Tamoxifen significantly downregulates the expression of ETV4 and ETV5, which are known to play a central role in stem cell renewal and differentiation.
Gastrointestinal stromal tumors	ETV1	trifluoperazine and thioridazine	/	GIST882	Trifluoperazine and thioridazine are potential ETV1 targeting drugs. Combined of phenothiazine and MEK inhibitors exerts strong anticancer effect in GISTs.
Cervical carcinoma	ETV1	p-anisidine	/	HeLa	p-anisidine is a promising anticancer agent targeting ETV1 with an IC50 of 27.769 mg/mL in HeLa cells.

GIST, gastrointestinal stromal tumors; GI-LMS, gastrointestinal leiomyosarcomas.