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Review Article

Regulation of ETS family of transcription factors in cancer

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Abstract

E-26 Transformation Specific (ETS) transcription factors are known to cause various cancers and their aberrant expression has been related to various oncogenic processes like metastasis and angiogenesis. Currently very few drugs exist which can directly target oncogenic transcription factor and none of them are approved for human use. To design ETS transcription factor targeting small molecules, an understanding of their regulation in cancers is essential. In this review, we have discussed upstream transcriptional regulations of ETS factors that includes epigenetic alterations in DNA like methylation and acetylation, alternate promoter, fusion gene formation, promoter affinity/specificity, recruitment of cofactors/repressors, etc. Additionally, we have also detailed the regulatory post translational modifications like phosphorylation, acetylation and ubiqutinylation for various ETS family members. These transcriptional and translational alterations regulate the expression of all ETS family members and can provide rational for drug designing in future.

Keywords: ETS, Transcription, Phosphorylation, Acetylation, Ubiqutinylation, Regulation

Introduction- The ETS Family History

ETS1; the first E-Twenty-six Transformation Specific transcription factor member capable of cellular transformation; was first discovered and characterized in the early eighties by several groups [1-3]. Since then, more than 7,500 scientific articles have made their entries in National Library of Medicine (PubMed search) for the term 'ETS Transcription Factor', indicating the immense importance of these factors in biological sciences and diseases (**Figure 1**). These metazoan specific proteins consists of 12 subfamilies sharing a conserved 85 amino acid long DNA binding domain called the 'ETS domain' which recognizes a consensus purine rich GGA(A/T) core [4,5].Till date based on conserved sequence homology and functions, 28 ETS family members in humans (27 in mice) were identified (**Figure 2**) [6,7]. ETS family have various physiological roles like hematopoiesis, immune cell maturation, neuronal and vascular development which were prominent in knock out mouse models (**Table 1**) [6]. However, in context of cancers most ETS family members are considered to be oncogenic capable of transformation. Overexpression of important ETS factors like ERG, FLI1, ETS1, ETV1, ETV4/5/6, ELK, SPi1, are directly involved in initiation of leukemias, prostate cancer, breast cancer, sarcomas, astrocytoma, hepatic carcinoma, melanomas, etc. [8-20]. Additionally, these ETS factors also regulate various oncogenic processes like angiogenesis, invasiveness, epithelial mesenchymal transition (EMT), stemness, metabolic reprogramming, immune evasiveness, deregulation of checkpoints, etc. by activation or repression of their target genes [14,17,19,21-27]. In this review, we will focus on regulation of ETS transcription factors in cancers.

Family Hierarchy: Transcriptional Regulation of ETS Factors in Cancers

All gene expressions are regulated at their promoters by various transcription factors, DNA modifications, cofactors and enhancers. Deregulation of transcription factor binding at promoters often triggers cancer initiation [64-67]. Regulation of ETS family members is modulated by various mechanisms of transcriptional regulation like promoter methylation/acetylation, promoter replacement by gene fusion formation, activation/repression of upstream cofactors/transcription factors, alternate promoter activation/specificity; which are represented in **Figure 3**. Since ETS family consist of a large number of genes, we will focus on a few important transcriptional regulatory mechanisms of ETS members that are involved in human cancers.

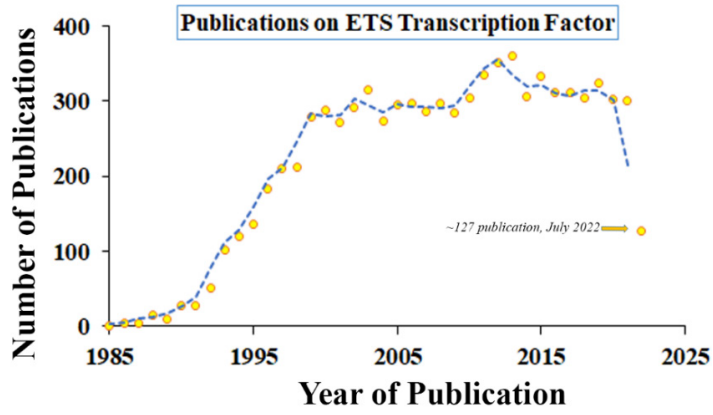

Figure 1. Publications on ETS transcription factors with respect to timeline.

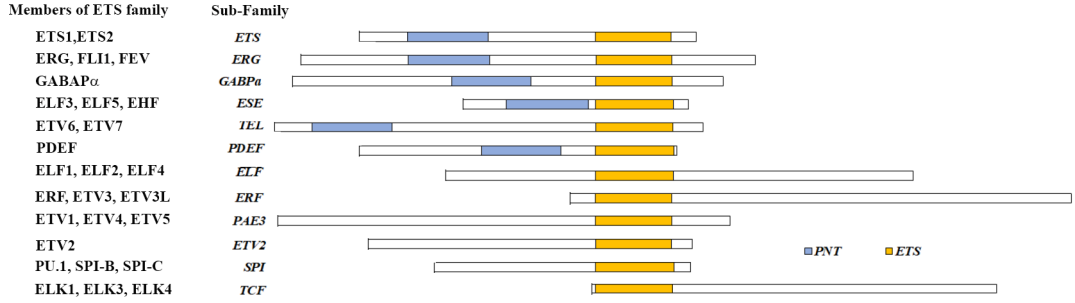

Figure 2: ETS family members with conserved domains.

Table 1. Functional Genetics of ETS transcription factors: Mouse models.

ETS Factor	Phenotype/physiological role in knock-out mice	Refs
ETS1	T cell survival, activation and maturation defects, Defects in B cell auto immune response, NK cells lineage defects, vascular inflammation and remodeling defects, endothelial cell survival defects, congenital and developmental defects of kidney.	[28-34]
ETS2	Extra embryonic membrane defects, endothelial cell survival defects, Thymocyte maturation defects.	[32,35-37]
ERG	Defects in angiogenesis	[38]
FLI1	Disruption of hematopoietic lineage	[16]
ETV1	Arterial remodeling and Arrhythmia	[39]
ETV 2	Lack of hematopoietic and hematoendothelial lineage; Defects in vasculogenesis	[40-44]
ETV 4	Estrogen signaling in endometrium	[45]
ETV 5	Defects in spermatogenesis; breakdown of cellular homeostasis in alveolar type II(AT2) cells	[46,47]
ELK 1	Development of male sterility	[48]
ELK 4	Defects in thymocytes	[49]
ELK 3	Increased synthesis of nitric oxide (Reactive nitrogen species); delayed post-natal retinal angiogenesis in mice	[50,51]
GABPα	Encouraged invasion and metastasis in papillary and follicular thyroid carcinoma	[52,53]
ELF 1	Reduced transcriptional responses to cytokine interferon-β	[54]
ELF 4	Causes autoinflammatory and immunodeficiency diseases	[55]

ETV 6	Defects in embryonic hematopoiesis	[56]
Spi B	Inhibition of plasmacytoid dendritic cell development	[57]
Spi C	Defective inflammatory response and iron metabolism in macrophage	[58]
Spi 1	Retardation of erythropoiesis	[59]
Erf	Maintained embryonic stemness, highly expressed pluripotency	[60]
Elf 3	Severe alteration of tissue architecture in small intestine, poor villus formation, abnormal morphogenesis, terminal differentiation of absorptive enterocytes	[61]
Elf 5	Absence of alveologenesis	[62]
SPDEF	Lack of conjunctival goblet cells and formation of dry eye	[63]

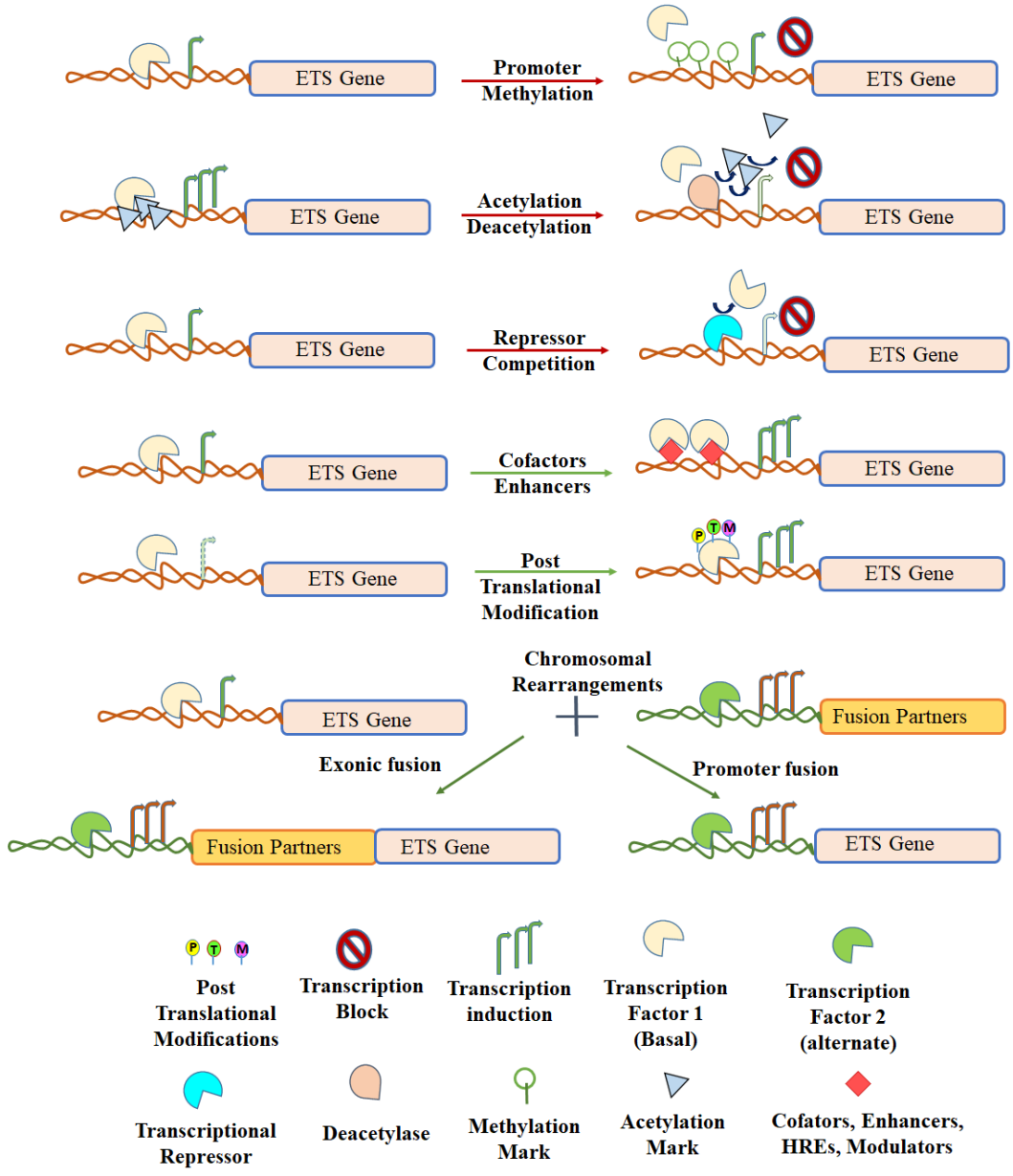

Figure 3: Mechanisms of regulation: ETS factors.

ETS family members; ETS1 & ETS2

The TATA box less *ets1* gene, is regulated positively at its promoter by upstream regulatory factors like AP1, AP2, HIF2alpha, and ETS1 itself [68-70]. Other growth factors like, TNF-alpha, HGF can indirectly induces ETS1 mRNA in cancers [71,72]. Interestingly, Retinoic acid was shown to alter *ets1* expression in both positive and negative manner with context of cell milieu [73-75]. Recently, Nf-KB1 and Nfatc2 was shown to bind ETS1 promoter resulting in its up regulation and promotion of breast cancer invasiveness [76]. As a negative regulator, tumor suppressor p53 was shown to repress ETS1 expression [77]. In parallel, *ets2* gene is transcriptionally repressed by v-Myb and ERF in various cancers [78,79].

ERG family members; ERG, FLI1, FEV

ERG is known as a primary driver in many cancers. Interestingly, 30 transcript variants of ERG have been identified due to multiple promoters and their epigenetic regulation via methylation [80-82]. Surprisingly, ERG can form gene-fusion with other gene promoter or regulatory elements like TMPRSS2, EWS, TLS/FUS etc. resulting in deregulation of ERG fusion transcripts in prostate cancer, Ewing sarcoma, leukemia [15,50,83-90]. Occasionally, ERG fusions can drive wild type ERG's transcription [91]. Similarly oncogenic FLI1 can form fusions with other genes like EWS, FUS, etc resulting in aberrant expression of FLI1 in cancers like Ewing sarcoma [92]. Wild type FLI1 promoter is induced by ETS1, ETS2, ELF1 or FLI1 itself in a GATA factor dependent manner, but is inhibited by ETS factor Tel/ETV6 [93-95]. FLI1 is regulated by ETV2 in a feed forward loop where both ETV2 and FLI1 can upregulate FLI1 transcriptionally [96]. ETS factor coding the *FEV* (Fifth Ewing Variant) gene is regulated by transcriptional activation of GATA sites at its promoter [97]. Interestingly, FEV is implicated as a tumor suppressor and is down regulated in prostate cancer [98]. FEV translocation (2;16) with either FUS or ETV1 generates a high expressing FUS-FEV or FEV-ETV1 fusion gene in <10% of Ewing sarcoma [99,100].

ESE family members; ELF3, ELF5

ELF3 (ETS transcription factor 3) is transcriptionally induced in trophoblasts by EVT-specific super-enhancers [101]. In lung adenocarcinoma, ELF3 locus is often amplified and hypomethylated resulting in increased expression [102]. While high ELF3 expression promotes epithelial mesenchymal transitions in liver cancer and breast cancer, the role is reversed in case of ovarian cancer [103-107]. ELF5 (ETS transcription factor 5) expression in embryonic stem cells and breast epithelial cells are regulated by promoter methylation resulting in lineage determination and mammary gland development respectively [108-110]. ELF5 owing to multiple promoter have tissue specific expression which are often deregulated in cancers [108,111]. ELF5 promotes basal phenotype in breast cancer by inhibiting ERalpha and Foxa1 [112,113]. Additionally, ELF5 was shown to inhibit breast cancer metastasis and EMT by transcriptionally repressing factors like SNAIL2, CD24 indicating a diabolic behavior in oncogenesis [114,115].

TEL family members; ETV6

ETV6 or TEL (Translocation ETS Leukemia) is often deregulated in leukemia, colorectal and breast cancer [79,116-118]. Deficiency in ETV6 expression often results in thrombocytopenia and patients are often predisposed to leukemia [119]. Promoter methylation or regulation via other factors like AKIRIN1, COMMD9, DYRK4, JUNB, and SRP72 have been implicated in regulating ETV6 expression in metabolism and cancers [120,121]. Recently, RBPJ protein was shown to transcriptionally regulate ETV6 and its fusion in glioblastoma [122]. ETV6 can form more than 30 types of gene fusions in various cancers [123,124]. Factors regulating wildtype ETV6 promoter might also regulate ETV6 fusion genes like ETV6-NTRK3, ETV6-RUNX1 and ETV6-JAK2 in various cancers [122,125-128].

ELF family members; ELF1, ELF2

ELF1 (E74-like factor 1), associated with erythroid maturation can be regulated at its promoter by transcription factor PU.1 [129]. Rb gene was reported to interact with ELF1 inhibiting T cell activation by down regulation of ELF1 transcription program [130]. ELF1 acts as tumor suppressor in prostate cancer; as deletion of ELF1 results in senescence and increased docetaxel susceptibility [131]. On the contrary, ELF1 promotes glioma development by activating GFI1/FBW7 axis via MEIS1 factor indicating cancer specific roles [132]. Not much is known about regulation of ELF2 in cancers except that it is involved in processes like angiogenesis and invasiveness [133,134].

PEA3 members; ETV1, ETV4, ETV5

Homologues of ETV1/4/5 forms the PEA3 family which are involved in various cancers [135]. Although ETV1 (ETS variant 1) is mainly regulated by androgen, other factors like postnatal maturation gene signaling also contribute to regulation of its expression [21,136,137]. ETV1 can regulate various oncogenic properties in cancers of prostate, colorectal, breast, etc [12,137-140]. Additionally, ETV1 gene can form fusions with inducible promoter of TMPRSS2, OR51E2-ETV1, EWSR1-ETV1 and regulates various cancer [90,141,142]. Whereas ETV4 can regulate its own transcript expression in a tissue dependent manner in various cancers [143-146]. ETV4 can also form fusions like TMPRSS2-ETV4, SLC45A3-ETV4, DDX5-ETV4, FUS/ETV4, NCOA2-ETV4 in various cancer [99,141,147-149]. Similarly, ETV5 expression is regulated by ALK in a MAPK dependent manner in neuroblastoma [150]. Promoter methylation of ETV5 also upregulates it's expression in colon cancer [151]. ETV5 promotes oncogenic processes like myometrial infiltration in endometrial cancer, proliferation and anchorage independent growth, cell adhesion in ovarian cancer [152-154]. ETV5 also forms fusion in prostate cancer with partners like TMPRSS2 and SLC45A3 [155].

ELK family member; ELK1, ELK3 and ELK4

ELK1(ETS Like-1) expression is regulated by factors like ERK kinase in association with TCF-SRF (serum response factor) complexes in astrocytomas, androgens in bladder cancer [156,157]. High ELK expression is associated with cancers of colon, urinogenital and thyroid. ELK3 expression is up regulated by ribosomal kinase RSK2 or Ras/ERK pathways promoting cancers [158-160]. Hypoxia can downregulate ELK3 expression [161,162]. ELK4 among the members can form a SLC45A3-ELK4 fusion in prostate cancer regulated by androgen signaling [163]. ELK4 also promotes gastric cancer and glioblastoma through anti-apoptotic mechanism [164,165].

Family Business: Post Translational Modifications of ETS Protein Products in Cancer

Apart from ETS-DNA binding domain, which is conserved among all family members of ETS transcription factors, there are other important domains among the various members. For example, *Pointed* domain (PNT), which is present among ETS, ERG, GABPα, ESE and TEL sub-families is responsible for homo-oligomerization, hetero-oligomerization and transcriptional repression [166-168]. Other domains, includes the TAD (Transactivation domain) domain responsible for cofactor docking, activation/repression of transcriptional functions of ETS family members, B-box SRF interacting region responsible for enhanced DNA binding are found among members of ETS family [169-173]. Post translational modifications (PTMs) like phosphorylation, acetylation, ubiqutinylation, glycosylation etc., in protein domains are often associated with structure and function based regulation of transcription factors including ETS family in cancers [174]. Various PTMs of ETS transcription factor families represented across domains and families in **Figure 4** and their effect on function and regulation of these factors in cancer will be discussed below.

Phosphorylation: The bread winner

Various growth factors, stress, mitogenic signals activate serine/threonine kinase MAPK/ERK; which are known to phosphorylate various ETS family members and initiate their functions in cancers. For example; transcription factor ERG was shown to be consecutively phosphorylated by ERK kinase at Serine 215 (S215) and S96 residue resulting in loss of EZH2-Suz12 polycomb repressor complex and activation of ERG mediated metastatic program in prostate cancer [175]. Recently, AKT kinase directed modulation of ERK -ERG phosphorylation axis was identified; where presence of active AKT dictates luminal fates of prostate cancer cells instead of EMT program [176,177]. Meanwhile MAPK/ERK2 kinase can phosphorylate ERG oncoprotein; resulting in hematopoietic stem and progenitor cells (HSPCs) proliferation and activation of oncogenic programs in acute myeloid leukemia (AML) and T-acute lymphoblastic leukemia (T-ALL) [178]. Although other members of the subfamily;

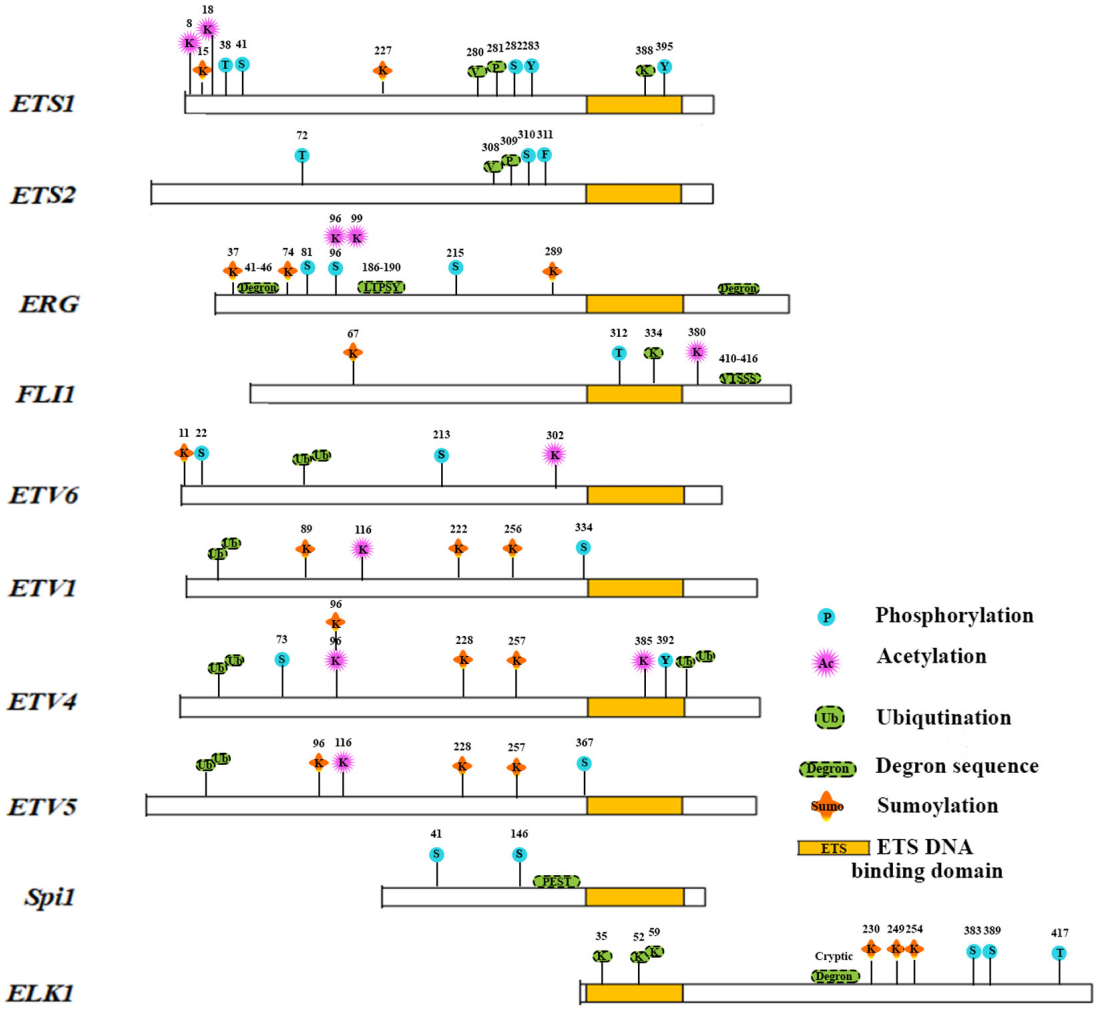

Figure 4: Post Translational Modifications of ETS family proteins.

FLI1 and FEV were shown to be *in vitro* phosphorylated by MAPK/ERK, there is no direct role of ERK phosphorylation on regulating FLI1 or FEV mediated oncogenesis [179]. MAPK/ERK kinases not only phosphorylates ETS subfamily members ETS1 and ETS2 in various cancers but are also transcriptionally regulated by ETS1/2 for maintenance of cancer program [180-182]. ETS1 phosphorylation at Threonine38 (T38) and S41 via ERK results in CBP/p300 mediated transcriptional activation, increased invasiveness and EMT in breast cancer [180,183-186]. While ETS2 phosphorylation by ERK1/2 were prominent in tamoxifin resistance breast tumors [187]. Multiple phosphorylation by MAPK/ERK cascade are also reported in other family members like i) Phosphorylation at S383,S389, T417 residues of ELK1 oncoprotein resulting in enhanced transactivation, proliferation, anti-apoptotic mechanisms and metabolic reprogramming in diverse cancers [173,188-192] ii) Phosphorylation at S73 residue of ETV4 (Pea3 subfamily) oncoprotein resulting in stabilization of ETV4 via blockage of ubiquitinylation signals in colorectal cancers [193]. While phosphorylation of another Pea3 family member; ETV1 oncoprotein in the activation domain (90-160 amino acid) resulted in activation of ETV1 transcriptional program in various cancers [194,195].

Other than mitogen activated kinases, depending upon cell milieu; various kinases affects ETS factor phosphorylation and subsequent function/regulation in cancers. For example; i) calcium signaling modulators CAMP kinases act as inhibitory signals, as CAMKII mediated phosphorylation inhibited transactivation of both ETS1 and ETS2 family members via multiple phosphorylation adjacent to DNA binding domain [196-199]. Interestingly, crosstalk between multiple phosphorylation are needed for complete inhibitory effects [196,197]. ii) AGC kinase family members like PKA, PKC kinases have been reported in phosphorylation of ETS factors. Both ETS1 and ETS2 proteins are stabilized and activated by PKC kinase in various cancers [200,201]. While ERG subfamily member FLI1 was phosphorylated at Threonine 312 (T312) by PKC delta kinase in a c-abl dependent manner resulting in FLI1 activation, stem cell differentiation and immune modulation [202-204]. PKC alpha mediated phosphorylation of Pea3 sub family members ETV1 and ETV5 at S334 and S367 respectively altering their DNA binding specificity towards high/low affinity promoters results in tumorigenic signaling [205,206]. iii) Src kinase mediated phosphorylation of ETS1/ETS2 at tyrosine 283 (Y283)/ Phenylalanine 311 (F311) has been implicated in various cancers [207]. Src mediated phosphorylation prevents binding and subsequent ubiquitinylation of ETS factors by COP1 E3 ligase [207,208]. iv) SPI sub family member Spi-1/PU.1 was reported to be phosphorylated by AKT kinase at S41 resulting in transactivation [209,210]. While Spi-B was reported to be phosphorylated by Casein Kinase II at multiple sites (S37, S129, S144 and S146) resulting in increased protein stability and decreased transactivation in cancers [211].

Acetylation: The frugal son

Acetylation of transcription factors including ETS family members often dictates subcellular distribution, DNA affinity, stability, transcriptional activity and results in cancers [212-215]. The pioneer member ETS1 is acetylated and dissociated by p300 (histone acetyl transferase; HAT) from chromatin during activation of miR-192 [216,217]. Again, ETS1 can be acetylated by CBP (HAT) at lysine 8 (K8) and K18 within the N-terminal domain, facilitating interaction with BRD4 and activating VEGF mediated angiogenesis program [218]. ERG is acetylated by p300 at K96/K99 residues promoting BRD4 regulated hematopoietic transcriptional program in acute myeloid Leukemia and invasiveness in case of prostate cancer [219,220]. Other ERG subfamily member FLI1 was reported to be acetylated at lysine 380 by p300/CBP-associated factor (PCAF) resulting in decreased FLI1 stability and DNA binding affinity [221]. While HDAC1 was identified as a deacetylase for FLI1 increasing DNA binding and transcriptional program associated with FLI1 directed oncogenesis [222]. On the contrary, EWS-FLI1 chimeric oncoprotein, is acetylated by both p300 and PCAF at the C-terminal FLI1 domain (at K240, K252, and K380 lysine number corresponds to wildtype FLI1) resulting in stronger DNA binding and transcriptional activation of FLI1 [223]. Pea3 family members ETV1 and ETV5 are acetylated by p300/PCAF at K116 residue resulting in transactivation and stability of the oncoproteins [114,224,225]. While Pea3 member ETV4 exhibits multiple p300 mediated lysine acetylation promoting transactivation functions [226,227]. Other acetylation include, HAT Tip-60 mediated acetylation and co-repression of ETV6/TEL that mediates transcriptional programs [228] and p300 mediated acetylation and subsequent ubiquitinylation of ELF5 in breast cancer [229].

Ubiquitylation & sumoylation: The prodigal son

Protein turnover is often regulated via proteasomal pathway via PTMs like ubiquitylation and sumoylation. Ubiquitin moiety can bind to lysine(K) residues within proteins creating mono (K63) or poly(K48) ubiquitin chains, which may then act as signals for proteasomal or other pathways [230-232]. The turnover of ETS factors are tightly regulated by crosstalk between PTMs resulting in ubiqutination mediated degradation. For example, COP1 E3 ubiquitine ligase has been reported to ubiqutinylate various ETS factors at specific valine(V)/proline(P) residue pairs followed by phosphorylation events. ETS1 and ETS2 are poly-ubiquitinylated at V280/P281 and V308/P309 residues following serine phosphorylation resulting in their proteasomal degradation by E3 ubiquitin ligase COP1 [207,231,233]. In fact ETS1 and ETS2 are protected from this ubiquitinylation by consecutive phosphorylation at their adjacent sites S282/Y283 and S310/Y311 by CAMKII and SRC kinases [231]. PEA3 family members ETV1/ETV4/ETV5 are also subjected to poly-ubiqutinylation at V/P sites and subsequent proteasomal degradation by COP1 [234,235]. Interestingly, COP1 is suggested to act as a tumor suppressor and prognostic marker and its deregulation has been reported in many cancer [235-239]. ERG family proteins lacking COP1 binding sites are resistant to COP1 mediated ubiqutinylation [235]. However, E3 ubiqutine ligase SPOP (Speckle-type POZ protein) has been reported to degrade ERG by ubiqutinylation of specific degron motifs at N-terminus(41-46 amino acid) and C-terminus (23-27 a.a) of ERG resulting in suppression of ERG positive prostate cancer progression [240,241]. ERG can be degraded by SCF E3 ligase complex where a typical phospho degron (^{186}LTPSY^{190}) is recognized by the ligase for ubiquitination [242,243]. ERG Family members; FLI1 is also ubiqutinylated at K334 in its wild type form and at residue K380 when it exists as the EWS-FLI1 fusion oncoprotein [244]. Recently it is observed that, SPOP E3 ligase can regulate both FLI1 and its fusion protein's turnover by binding to a VTSSS" degron motif of EWS-FLI1/FLI1 (462-468aa/410-416aa), which is a prerequisite for

polyubiqutinylation and subsequent proteasomal degradation [245]. While TEL family member ETV6 is ubiquitinylated at SAM domain by F-box family ligase FBXL6 resulting in proteasomal degradation [246,247]. ELK1 can be a substrate for both poly and mono ubiqutinylated [248]. ELK1 is reversibly mono-ubiqutinylated at site K35, K52, K59 resulting in impaired DNA binding activity [249]. While F box ubiquitine ligase, FBXO25 can poly ubiqutinylate ELK1 at a cryptic degron motif (amino acids 167-196) resulting in its degradation [250,251].

SUMO (small ubiquitin-like modifier) based modification facilitated by the SUMO conjugation enzyme system results in sumoylation of protein leading to various signaling events. With a few exceptions, most ETS factors undergo transcriptional repression, degradation or loss of functionality upon sumoylation. For example, sumoylation of ETS1 at K15 and K227 residues by E2 SUMO-conjugating enzyme Ubc9 and a E3 SUMO ligase, PIASy results in defective transactivation without any effect on turnover of the protein [233]. In acute myeloid leukemia; ERG is hyper sumoylated at K37, K74, and K289 by PIAS4 SUMO E3 ligase resulting in enhanced stability of ERG protein [252]. On the contrast, ERG family member FLI1 fails to transactivation when sumoylated by sumo E3 ligase PIASxα/ARIP3 at K67 site [253]. All Pea3 family member ETV1/4/5 are known to be sumoylated [135]. These ETS factors are sumoylated at conserved lysine residues (K89/96, K222/228, and K256/257) resulting in their altered transcriptional efficiency [254,255]. Tel family member ETV6 is also sumoylated at K11 residue by PIAS3 ligase resulting in repression of ETV6 transcriptional activity [256]. Interestingly, UBC9, ubiquitin conjugating enzyme has been shown to promote ETV6 sumoylation resulting in localization to cell-cycle-specific nuclear speckles in leukemias housing a TEL/AML fusion [257]. ELK1's nucleus to cytoplasmic shuttling is modulated by sumoylation at K230, K249, or K254. Recently, ELK1 transactivation was connected to p38MAPK mediated phosphorylation, which promotes sumoylation and downregulation of activity [258]. PTMs like Ubiquitination and sumoylation in transcription factors are strictly regulated and as with others, deregulation of these PTMs results in enhanced activity of ETS family in various cancer [259-261].

Few other types of PTMs like methylation and glycosylation are also reported for a few ETS factors. In prostate cancer, TMPRSS2-ERG fusion oncogenic activity is induced by EZH2 mediated methylation of the oncoprotein at K362 residue [262]. Activation of the Ets transcription factor Elf-1 requires multiple glycosylation in patients with lupus disease [263].

Conclusion, Be Careful of that Family

Owing to their implications in cancers, ETS family of transcription factors are important drug targets at present [264,265]. However, ETS factors also have physiological roles, thus off target effects of drugs should be considered during drug selection [266-268]. Interestingly, ETS factors like ERG, ETV1, FLI1, ETV6, etc., can form gene fusions which acts as drivers of many cancers [269,270]. These fusions are active drug targets and various inhibitors/drugs against these fusion ETS factors are listed in **Table 2**. A few studies on ETS regulation based on cellular milieu also indicated unknown factors that might play vital role

Table 2. Drugs against ETS Fusion genes in cancers.

Drugs	ETS fusion target	Cancer	Mechanisms	Ref.
TK-216	EWS-FLI 1	Ewing sarcoma	Decrease oncogene expression and increase tumor suppressor genes, induce apoptosis NCT02657005	[274]
Englerin A	EWS-FLI 1	Ewing sarcoma	Induction of cell cycle arrest and cell death; Inhibition of cell proliferation; reduction of EWS-FLI 1 phosphorylation and DNA binding	[264]
Midostaurin (PKC412)	EWS-FLI 1	Ewing sarcoma	Inhibited cell growth and promoted apoptosis	
Mithramycin	EWS-FLI1	Ewing sarcoma	Causes repression of H3 acetylation and association with EWS-FLI1 protein thereby reduction in oncogenesis	[275]
Trabectedin	EWS-FLI1	Ewing sarcoma	Inhibits the expression of EWS-FLI1 and tumor associated macrophage	
Trabectedin + Oliparib	EWS-FLI1	Ewing sarcoma	Inhibits the expression of EWS-FLI1	
JQ 1	EWS-FLI1	Ewing sarcoma	Decreased proliferation, increased apoptosis and tumor formation inhibited	
YK-4-279	EWS-FLI 1	Ewing sarcoma	Inhibition of recruitment of co-activator molecule DHX9 for neoplastic transformation	[276]
Resveratrol	DDX5-ETV4	Prostate cancer	Degrades the DDX5 protein and inhibit mTOR pathway	[277]
JQ 1	TMPRSS2-ERG	Prostate cancer	Disrupt association between bromodomain containing domain (BRD4) with androgen receptor (AR) and inhibit transcriptional activity of AR and TMPRSS2-ERG expression	[275]

siRNA-loaded liposome	TMPRSS2-ERG	Prostate cancer	Inhibition of angiogenesis and cell proliferation; Induction of apoptosis	[278,279]
siRNA	TMPRSS2-ERG	Prostate cancer	Decreased cell proliferation and migration thereby metastasis; increased apoptosis	[280]
Taxol	TMPRSS2-ERG EWS-ERG FUS-ERG	Prostate cancer Fibroblast sarcoma	Caused genetic instability by aneuploidy	[281]
Larotrectinib	ETV6-NTRK3	Breast cancer	Inhibition of tropomyosin kinase inhibitor (TKI) demonstrates stoppage of metastasis	[282]
Entrectinib	ETV6-NTRK3	Breast cancer	Inhibition of tropomyosin kinase inhibitor (TKI) demonstrates stoppage of metastasis	
Nutlin-3	ETV6-RUNX1 (E/R)	Childhood leukemia	Inhibits E/R induced MDM2-p53 interaction promoting cell cycle arrest and apoptosis	[283]
Valproic acid	EWS-ERG EWS-FLI1	Ewing sarcoma	Reverses the actions of fused oncoprotein on RXRα transcriptional activity and subsequently cell growth inhibited	[284]
Furamidine	ETV6-NTRK3	Glioblastoma	Binds with DNA binding domain of RBPJ (an upstream regulator ETV6-NTRK3) thereby productions of ETV6 and ETV-NTRK3 are prevented	[122]

during chemotherapy. For example, glutamine starvation can reduce expression of ETS1 and alter its translocation, thereby reducing its transcriptional activity in ovarian cancers [271]. Alternatively, in a hormone dependent cancer like prostate, androgens rich environment provides induction for TMPRSS2-ERG [272]. This can be advantageous during chemotherapy, as it is reported that phosphorylation of ERG fusions during DNA damage results in its degradation; independent of androgen response [242]. Recently, metabolic coactivator PGC1-alpha was reported to induce ERG fusions transactivation during metabolic stress in cancers indicating a metabolic vulnerability during resistant cancer development [273]. Thus, modern day cancer therapy targeting ETS transcription factors must take into account the cellular milieu and stress response during drug designing.

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Authors Contribution

A.D., and N.S. were responsible for conceptualization, manuscript design, data curation and graphics. S.G., A.D. and N.S. were responsible for writing and editing.

Competing Interests

The authors declare no competing interests. Correspondence and other requests regarding the work should be addressed to N.S.

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