Oncogene (2000) 19, 6514–6523
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www.nature.com/onc

Regulation of Ets function by protein–protein interactions

Runzhao Li*[,1,2,4], Huiping Pei[1,4] and Dennis K Watson[1,3,4]

[1]*Center for Molecular and Structural Biology, Medical University of South Carolina, Charleston, South Carolina, SC 29425, USA;* [2]*Department of Medicine, Medical University of South Carolina, Charleston, South Carolina, SC 29425, USA;* [3]*Department of Pathology and Laboratory Medicine, Medical University of South Carolina, Charleston, South Carolina, SC 29425, USA;* [4]*Hollings Cancer Center, Medical University of South Carolina, Charleston, South Carolina, SC 29425, USA*

Ets proteins are a family of transcription factors that share an 85 amino acid conserved DNA binding domain, the ETS domain. Over 25 mammalian Ets family members control important biological processes, including cellular proliferation, differentiation, lymphocyte development and activation, transformation and apoptosis by recognizing the GGA core motif in the promoter or enhancer of their target genes. Protein–protein interactions regulates DNA binding, subcellular localization, target gene selection and transcriptional activity of Ets proteins. Combinatorial control is a characteristic property of Ets family members, involving interaction between Ets and other key transcriptional factors such as AP-1, NFκB and Pax family members. Specific domains of Ets proteins interact with many protein motifs such as bHLH, bZipper and Paired domain. Such interactions coordinate cellular processes in response to diverse signals including cytokines, growth factors, antigen and cellular stresses. *Oncogene* (2000) **19,** 6514–6523.

Keywords: protein–protein interaction; Ets; transcriptional modulation; combinatorial control

Introduction

Transcriptional regulation is dependent upon interactions between nuclear proteins. Protein–protein interactions are involved in every step of cell signaling, including receiving of signal, selection of target genes, regulation of DNA binding ability, regulation of transcriptional activity and turn-over of transcription factors. Ets proteins are a family of transcription factors which play roles in important biological processes, including cellular proliferation, differentiation, development, transformation, immune response and apoptosis. (Bhat *et al*., 1996; Ghysdael and Boureux, 1997; Graves and Petersen, 1998; Watson *et al*., 2001): Structural analyses have demonstrated that most Ets proteins bind DNA as monomers (Kodandapani *et al*., 1996; Liang *et al*., 1994; Werner *et al*., 1995), unlike many other well-known families of transcription factors that can bind DNA as homo-or heterodimers. The transcriptional activity of Ets proteins is modulated by other factors/partners (Bhat and Papas, 1994; Crepieux *et al*., 1994). Functional interaction between Ets proteins and other factors have been observed and plays an important role in many biological processes. However, many physical interactions cannot be demonstrated by direct binding assays due to the weak affinity, transient binding or absence of required cofactors, such as DNA or a third partner. In recent years, based on the improved technologies, such as two hybrid interactive screens, many novel proteins have been identified as Ets family partners. Evaluation of the physical interaction and correlation with function has greatly advanced our knowledge on regulation of eukaryotic gene transcription. The network of Ets control is emerging from the studies of Ets interacting proteins. This review will examine some of the protein–protein interactions that have been identified and describe specific examples that establish correlation between Ets interacting partners and specific biological functions.

Regulation of DNA binding ability

DNA binding ability is the key property of all transcription factors. The modulation of DNA binding can be viewed as the first level of transcriptional control. Although most of Ets proteins bind to DNA as monomers, DNA binding activity is enhanced or modulated by other factors. The identified intramolecular regulatory regions have been localized to conserved domains found in most Ets family members (Graves *et al*., 1998). DNA binding can be increased by the removal of negative regulatory domains, such as exon VII of Ets1 (Fisher *et al*., 1994). Interacting proteins also can relieve the intramolecular inhibition of DNA binding capacity. Interaction of SRF with the carboxy-terminal region of the ETS domain of Elk1 increases its ability to bind to a subconsensus DNA binding site (Rao and Reddy, 1992). Similarly, formation of Ets1-CBF-DNA complexes increases the affinity of Ets1-DNA interactions and decreases the rate of dissociation of CBF from the TcR α and β enhancers, resulting in synergistic activation (Wotton *et al*., 1994). Exon VII of Ets1 and NRDB of PEBP2αB/AML1/CBFα2 are negative regulative domains. Direct interaction of these two regions leads to an increase of DNA binding affinity and subsequent transcription activity by both partners (Kim *et al*., 1999). The dynamic balance of the interaction between CBFα2 and either of its two alternative partners, Ets1 or CBFβ, is one example of combinatorial control of transcriptional regulation (Gu *et al*., 2000). The paired box transcription factor Pax-5 stabilizes the DNA binding of Ets1, as well as PU.1, Elk-1 and Net to the mb-1 promoter. Both Pax-5 and Ets binding sites are necessary for ternary complex formation (Fitzsimmons *et al*., 1996). It has been recently demonstrated that the amino-terminal sub-

*Correspondence: R Li, CMSB, Room 315, Hollings Cancer Center, Medical University of South Carolina, 86 Jonathan Lucas St. Charleston, South Carolina, SC 29425, USA.

domains of Pax specifically interact with the DNA binding (ETS) domain of Ets1 and the ability to recruit Ets proteins to bind Pax/EBS (Ets Binding Site) composite site is a property of multiple Pax proteins (Wheat *et al*., 1999). The bHLH zipper proteins, TFE3 and USF, also enhance binding of Ets proteins to EBS by relieving the intramolecular inhibition via direct protein–protein association (Tian *et al*., 1999).

Target gene selection

Functional transcription is often dependent upon the selection of suboptimal nucleotide sequence(s) present in the target gene. The lineage-specific and inducible expression of eukaryotic genes is controlled by assembly of multipartite complex of transcription factors on regulatory regions composed of sequence-specific protein binding sites. Protein–protein interactions direct Ets family members and other transcriptional factors to act on promoters/enhancers to increase transcription of Ets target genes. Physical interaction of Ets1 with GHF-1 is required for establishing lactotroph-specific PRL gene expression (Bradford *et al*., 1995). The Ets1-GHF-1 synergy requires a composite Ets1-GHF-1 cis-element, which exist only in the PRL promoter but not in GH promoter (Bradford *et al*., 1997). This synergy is one of the mechanisms by which different cell or tissue specific responses to identical signals is controlled. Several examples demonstrate that tissue-specific gene expression is achieved via the combinations of specific sets of transcription factors unique to each cell lineage or stage of differentiation. The interaction of Ets1 with tissue-restricted PEBP2αB/AML1 leads to a context-dependent transcription regulation (Kim *et al*., 1999). Pip (interferon regulatory factor) binds to its appropriate DNA element only in the presence of PU.1 (Eisenbeis *et al*., 1995). Phosphorylated PU.1 recruits Pip to form a ternary complex with specific EBS/Pip sequences in the promoter region of the Ig κ light chain gene (Brass *et al*., 1996; Ortiz *et al*., 1999; Perkel and Atchison, 1998). This specific combination of transcription factors coordinates protein–protein and protein-DNA interactions and confers cell type specificity to cytokine signals. Complexes formed between either Ets1 or Ets2 and Stat5 in response to IL-2 in T lymphocytes may control gene expression via binding to interferon γ activated site (GAS) motifs (Rameil *et al*., 2000). Functional cooperation can also be found among Stat1 and PU.1 on the FcγRI promoter in response to glucocorticoid stimulation (Aittomaki *et al*., 2000). It is known that the transcriptional activity of Tax1 on the HTLV-I LTR is modulated by the cooperative interactions between NFκB, Ets1 and Tax1 (Gitlin *et al*., 1993; Seeler *et al*., 1993). The Tax/Ets1 cooperative effect on the PTHrP P2 promoter is based on the ability of Tax, Ets1, and Sp1 to form a quaternary complex on the template DNA. Tax facilitates the interaction of Ets1 and Sp1 and participates directly in the transcription initiation process (Dittmer *et al*., 1997)

Ternary complex formation

Ets proteins are targets for phosphorylation in response to stimulation mediated through receptors, including, growth factor receptors, and integrin signaling. Ets proteins, like other transcription factors, associate with other proteins to form ternary complexes with DNA, thereby selecting the relevant target gene in a particular cell type. Three ternary complexes factors (TCFs), Elk1, Sap1a, and Net/Sap2 were originally identified (Wasylyk *et al*., 1998; see article in this issue by Yordy and Muise-Helmericks). The regulation of TCFs activity is an important mechanism by which the serum response element responds to growth factor signals (Treisman, 1994). The TCF subfamily of Ets transcription factors are conserved from *Drosophila* to human and represent key nuclear targets of MAP kinase pathways. A well-known example of such an interaction involves the regulation of the c-*fos* gene, where ELK1 forms a ternary complex with SRF and the SRE motif present in the promoter. This is an example of the fundamental importance of proto-oncogene cooperation in cellular growth control (Hipskind *et al*., 1991). The B-box of Elk-1 is both necessary and sufficient to mediate protein–protein interaction with SRF in the absence of the SRE (Shore and Sharrocks, 1994). In TCFs, the ETS domain is amino terminal and linked by a flexible spacer region to the SRF interacting region B-box (Janknecht *et al*., 1994; Ling *et al*., 1997; 1998). In response to MAP kinase signaling, the B-box of Elk-1 forms an inducible α-helix and provides a surface to interact with SRF, which augments the DNA binding ability of Elk-1 (Ling *et al*., 1997). Although able to bind the fos SRE, Delta Elk1, a variant of Elk-1 lacking the negative regulatory DNA binding domain (NRD), is unable to form a SRF dependent ternary complex with SRE and consequently cannot activate fos transcription (Rao and Reddy, 1993). It has also been demonstrated that Fli1 and EWS/Fli1 can function as TCFs, forming ternary complexes with SRF on Erg1 (Watson *et al*., 1997) and c-*fos* (Dalgleish and Sharrocks, 2000; Watson *et al*., 1997) SREs. In addition to the response to serum or MAP kinase signaling, an indirect interaction between Fli1 and RAR alpha has been demonstrated. In response to retinoic acid, these partners repress one another through an unknown 'bridging' factor (Darby *et al*., 1997).

Cooperation with other transcription factors

Sequences flanking the EBS not only partially define individual family member binding specificity, but also contains potential elements which may coordinate diverse cellular processes or mediate the cross-talk of different transduction pathways. Many transcription factors have their DNA binding sites adjacent to EBS. Depending on the precise sequence context, binding of Ets proteins near other transcription factors results in higher affinity interaction, synergistic repression or activation of specific target genes. Combinatorial control of transcriptional regulation is dependent upon the interactions between multiple nuclear proteins. Cooperation among Ets family members and other transcriptional factors has been demonstrated by inferred transcription of a large number of enhancer or promoter elements containing overlapping controlling elements.

Ets/AP-1 AP-1 is a transcription factor consisting of jun/fos family proteins and plays an important role in the signaling response to an incredible array of stimuli (Wisdom, 1999). Adjacent Ets and AP-1 binding sites occur in a large number of promoter/enhancer elements (Wasylyk *et al*., 1993; Westermarck and Kahari, 1999) and functional cooperation between Ets and AP-1 is critical for controlled expression of many genes, including cytokines (Gottschalk *et al*., 1993; Wang *et al*., 1994), MMPs (Crawford and Matrisian, 1996; Gutman and Wasylyk, 1990; Jayaraman *et al*., 1999), glutathione S-transferase (GST) Ya (Bergelson and Daniel, 1994; Crawford and Matrisian, 1996), viral genes (Nothias *et al*., 1993; Wasylyk *et al*., 1990), etc. The physical association between the DNA binding domain of Ets family proteins and AP-1 was demonstrated both *in vitro* and *in vivo* in activated human T cells (Bassuk and Leiden, 1995). Interaction of c-Jun with Elf1 results in formation of either a trimolecular complex or an Ets-AP1-DNA ternary complex after recruitment of c-Fos protein. Correlation between physical interaction of Ets1 with AP-1 and cooperative transcriptional activity was demonstrated using a c-Jun/c-Fos chimera protein, which is unable to interact with Ets proteins. GATA competes with c-Jun for binding to the $\beta3/\beta4$ site of PU.1 (ETS domain) and subsequently represses PU.1 transcriptional activity, indicating that the interaction between PU.1 and c-Jun is functionally important during hematopoietic cell differentiation (Zhang *et al*., 1999). Although other Ets proteins (Elf and Fli1) have been shown to interact with Jun via the ETS domain, the functional significance of these interactions were not demonstrated (Bassuk and Leiden, 1995). The expression of MMP genes are enhanced by a cooperative transcriptional activation between Ets1 and AP-1. It is interesting to note that synergistic transcriptional activation of tissue inhibitor of MMP (TIMP-1) can also be enhanced by the interaction between Ets1 and AP-1 (Logan *et al*., 1996).

Ets/NFκB NFκB is a ubiquitous transcription factor involved in immune, inflammatory and stress responses (Gilmore, 1999). Adjacent or overlapping binding sites for Ets and NFκB are present in many inducible lymphoid genes, including IL-2, IL2-receptor (John *et al*., 1995), IL-3 (Gottschalk *et al*., 1993), GM-CSF (Thomas *et al*., 1997), IL-12 (Gri *et al*., 1998), viral genes including the HIV-I enhancer (Seth *et al*., 1993) and signaling molecules, such as protein kinase CK2α (Krehan *et al*., 2000). Co-transfection of NFκB and Ets contributes to synergistic transcription activation of HIV-I and HIV-II (Bassuk *et al*., 1997), GM-CSF (Thomas *et al*., 1997), IL-2Rα (John *et al*., 1995) and IL-12 (Gri *et al*., 1998). These functional cooperations require the physical interaction between NFκB and Ets protein and other factors as well. Elf1 physically associates with the p50 subunit of NFκB and c-Rel/p65 *in vitro*, and the interaction between HMG-1Y and Elf1 may further stabilize the complex of Elf1/NFκB/HMG-1Y. (John *et al*., 1995). Leiden's laboratory has demonstrated that physical interaction between multiple Ets proteins (Ets1, Elf1 and PU.1) and NFκB are required for transactivation of HIV-I and HIV-II. The ETS domain of Ets1 is essential and sufficient for interacting with HD region of p50 subunit of NFκB, but not p65 (Bassuk *et al*., 1997)

Ets/bZIP factors Crystal structures of basic leucine zipper (bZIP) factors demonstrate that the basic region of bZIP factors mediates protein–DNA interaction, while the leucine zipper domain contributes to protein–protein interactions (Glover and Harrison, 1995). The coordination between two classes of transcription factors, Ets and bZIP, often plays a role in the expression of inflammatory response genes. The interaction between the ETS domain of PU.1 and the bZIP region of NF-IL6β results in the synergistic transcriptional activation of an artificial promoter containing both EBS and NF-IL6β consensus elements (Nagulapalli *et al*., 1995). However, the transcriptional activity of NF-IL6 was observed on the IL1β core promoter, in the absence of a DNA binding site for NF-IL6. It is believed that NF-IL6 is tethered by PU.1 to achieve transcriptional activation, designated protein-tethered transactivation (PTT) (Yang *et al*., 2000). PU.1 also tethers the bZIP transcription factor c-Jun, via interacting of ETS domain of PU.1 with basic domain of Jun, to enhance the transcriptional activity of the promoter of the M-CSF receptor gene (Behre *et al*., 1999). Furthermore, the Cytomegalovirus IE2 protein is tethered to PU.1 for activation of IL1β gene transcription (Wara-aswapati *et al*., 1999). The Epstein-Barr virus (EBV) nuclear antigen 3C protein (EBNA-3C) activates the LMP-1 promoter via interaction with PU.1 (Zhao and Sample, 2000). Thus, PTT is a mechanism by which Ets function can be extended by the combination with cell-specific transcription factors under defined conditions.

Ets/bHLH factors The basic helix–loop–helix (bHLH) transcription factors form homo- or heterodimers through their bHLH domains, enabling the basic regions to form a bipartite DNA-binding motif that recognize 'E-box', and play a crucial role in controlling of specific developmental processes (Murre *et al*., 1994). Although Ets-HLH synergistic activation was demonstrated previously (Rivera *et al*., 1993), physical interactions between bHLH transcription factors and Ets proteins has recently been proven. USF-1 interacts with the ETS domain of Ets1 via its HLH domain resulting in cooperative activation of HIV-1 expression. In contrast, several other Ets family members, including Elf1 and PU.1, do not interact with USF-1 (Sieweke *et al*., 1998). The consensus site of USF-1 and the TAD (Transactivation Domain) of Ets1 are essential for this activation of HIV-1. The binding of Ets1 in the absence of an EBS is another example of protein-tethered transactivation (PTT). The transcriptional synergy between the bHLH proteins E47 and TFE3 is dependent upon Ets1-mediated three protein-DNA complexes on the immunoglobulin μ heavy-chain gene enhancer (Dang *et al*., 1998). The NID (Net inhibitory domain) of Net/SAP2, a member of the TCF subfamily, interacts with the bHLH protein E47 through its HLH-like domain. This interaction is believed to change the conformation of Net/SAP2 and subsequently increased DNA binding (Maira *et al*., 1996).

Ets/Rb Elf1 protein contains a motif that is highly related to the Rb binding sites of several viral oncoproteins and binds to the pocket region of Rb both *in vitro* and *in vivo*. Elf1 binds preferentially to

unphosphorylated Rb and the phosphorylation of Rb results in the release of Elf1, which is correlated temporally with the activation of Elf1-mediated transcription (Wang *et al*., 1993). It is known that the pocket region of Rb interacts with many cell-cycle-control proteins such as cyclins and transcription factors (e.g., E2F, AP-1). The interaction between Rb and Ets may be important for the coordination of lineage-specific processes such as lymphokine production and lymphocyte activation. The Rb pocket domain, which is the binding site for the general transcription factor TFIID, can also bind to the N-terminus of PU.1, (Hagemeier *et al*., 1993). Recently, it has been demonstrated that GOOSECOID protein (GSC), a homoebox gene product, interacts with PU.1 via its N-terminal portion, which is also the binding site of Rb. Thus, GSC competitively inhibits the binding of Rb to PU.1, resulting in the suppression of blood formation in early embryogenesis (Konishi *et al*., 1999).

Since the ETS domain is highly conserved among all Ets family members, it is expected that several Ets family members may function on one gene simultaneously and the precise regulation of expression is achieved by this competition within the family. For example, synergistic transcription activation of MMP1 can be achieved by the interaction between ERG and AP-1 while ERG represses the transcriptional activation of MMP-1 by Ets2. This repression is dependent upon the physical interaction between ERG and Ets2 (Buttice *et al*., 1996; Basuyaux *et al*., 1997).

Co-factor

CBP/p300 is an adapter protein, bridging many specific transcriptional factors with components of the basal transcriptional machinery such as TFIID (Janknecht and Hunter, 1996). Both Ets1 and Ets2 recruit CBP/p300 to active the MMP promoter (Jayaraman *et al*., 1999; Watabe *et al*., 1998). Ets1 and CBP/p300 form a stable complex in a DNA independent manner and this complex possesses histone acetyltransferases (HAT) activity (Yang *et al*., 1998). Since CBP/p300 interacts with many transcription factors, the precise biological outcome is dependent upon on its partner. Interaction with histone deacetyltransferases (HDAC) provides a mechanism by which the partner of Ets can serve as a co-repressor, leading to transcriptional silencing. Interaction between CtBP and NET provides a bridge between NET and HDAC1 (Criqui-Filipe *et al*., 1999), leading to transcriptional repression. Similarly, it is known that Rb, which interacts with Elf1, physically interacts with histone deacetylase HDAC1 (Magnaghi-Jaulin *et al*., 1998). Another example is Sp1, which interacts with many Ets factors (Block *et al*., 1996; Dittmer *et al*., 1997; Eichbaum *et al*., 1997; Krehan *et al*., 2000)), and has been shown to interact with HDAC1 (Doetzlhofer *et al*., 1999), repressing transcription. TEL is able to recruit co-repressors such as SMRT and mSin3A resulting in transcriptional repression (Chakrabarti and Nucifora, 1999; Fenrick *et al*., 1999).

Conversion of activator to repressor

The mechanisms that control transcription factor switching between activator and repressor remain to be determined. However, interaction between Ets and other transcription factors results in either activation or repression of specific target genes. The factors that determine whether an individual Ets factor functions as an activator or repressor include composition of DNA sequence, presence of tissue specific factors, alternative splicing and the combinatorial control by multiple transcription factors. In contrast to the synergistic activation via the EBS/AP-1 elements present in the MMP1 and MMP3 promoters, binding of Ets proteins near the EBS/AP-1 of the polyoma virus enhancer represses AP-1 transcriptional activation (Goldberg *et al*., 1994). MafB, an AP-1 like protein, interacts with Ets1 in a DNA-dependent manner and inhibits Ets1-mediated transactivation of the transferrin receptor gene. This interaction inhibits erythroid differentiation (Sieweke *et al*., 1996). PU.1 also functions as a repressor by interacting with GATA-1, a zinc finger transcription factor required for erythroid differentiation. Both DNA binding and activation domains of PU.1 are required for inhibition of GATA-1-dependent transcription. The interaction between PU.1 and GATA-1 does not depend on the presence of consensus DNA sequences. GATA-1 seems not to affect DNA binding or transcriptional function of PU.1 (Rekhtman *et al*., 1999). GATA-1 also is a repressor of PU.1 function. A possible mechanism for this repression is competition between c-Jun and GATA-1 for interaction with the ETS domain of PU.1 (Zhang *et al*., 1999). In myeloid cells, GATA-1 represses myeloid gene expression, at least in part, through its ability to directly interact with the ETS domain of PU.1 and thereby interfere with PU.1 function (Nerlov *et al*., 2000). Transformation activity or cancer progression has been linked with the alteration of the Pointed domain. Substitution of the Pointed domains of ERG and Fli1 by EWS in the chimeric EWS-ERG and EWS-Fli1 results in strong transforming factor (Bailly *et al*., 1994; May *et al*., 1993). This may be in part due to ability of EWS-Fli1, but not Fli1, to interact with human RNA polymerase II (hsRPB7). HsRPB7 has characteristics of a regulatory subunit of RNA polymerase II and may influence promoter selectivity (Petermann *et al*., 1998). In contrast, the leukemia-associated t(12:21) translocation generates the Tel-AML1b chimeric protein. In this protein, gain of the Pointed domain converts AML1b from an activator to a repressor of transcription (Hiebert *et al*., 1996). These observations indicate that the Pointed domain may represent a specialized protein–protein interaction interface which is likely to be an important determinant of their specificity as transcriptional regulators though other partner (Fenrick *et al*., 1999 and article by Mavrothalassitis and Ghysdael in this issue).

We have recently demonstrated that Ets1 interacts with the Daxx protein, referred to as EAP1 (Ets1 Associated Protein 1) and the interaction of EAP1/Daxx with Ets1 causes the repression of transcriptional activation of model target genes (MMP1 and Bcl2) (Li *et al*., 2000). It remains to be determined whether Daxx/EAPI serves as a common co-repressor for additional Ets family members as well as for other transcription factors. The HLH protein Id2 interacts with either Elk-1 or SAP1 and disrupts ternary complex formation between Elk-1 or Sap1 at the c-fos SRE, blocking the cellular response to MEK

Table 1 Ets protein interactions

Partner	*Ets family*	*Target genes*	*Activity*	*References*
SRF	Elk1 SAP1a SAP1b Net Fli1	c-fos	A	Hipskind *et al*., 1991 Ling *et al*., 1997; 1998 Watson *et al*., 1997
SRF	Elk1/SAP1a Fi1/EWS-Fli	Erg1	A	Magnaghi-Jaulin *et al*., 1996 Watson *et al*., 1997
AP-1 (Jun)	Ets1	uPA		Bassuk and Leiden *et al*., 1995 Nerlov *et al*., 1992
c-Jun	Ets1	c-Jun	R	Goldberg *et al*., 1994
c-Jun	PU.1		A	Behre *et al*., 1999
AP-1	Ets1	TIMP-1	A	Logan *et al*., 1996
AP-1	Elf1	GM-CSF		Wang *et al*., 1994 Bassuk and Leiden *et al*., 1995
AP-1	Erg/Fli1	MMP1	A	Bassuk and Leiden *et al*., 1995 Buttice *et al*., 1996
c-Jun	Pointed	R7	A	Treier *et al*., 1995
c-Jun	YAN	R7	R	Treier *et al*., 1995
NFAT-1 (Fra-1/JunB)	Elf1	IL-2		Boise *et al*., 1993
MafB	Ets1	TfR	R	Sieweke *et al*., 1996
Myb	Ets1	CD13/APN	A	Shapiro, 1995
Pax-5	Ets1 Net Elk-1	mb-1	A	Fitzsimmons *et al*., 1996
Stat5	Ets1/Ets2			Rameil *et al*., 2000
NFκB	Ets1 Elf1 PU.1/Ets1	HIV-I, HIV-II IL-2Rα HTLV-I LTR	A	Bassuk *et al*., 1997 John *et al*., 1995 Gitlin *et al*., 1993 Seeler *et al*., 1993
HMG-1Y	Elf	IL-2Rα	A	John *et al*., 1995
NF-IL6β	PU.1	IL1b	A	Nagulapalli *et al*., 1995 Yang *et al*., 2000
Id2	ELK-1 SAP1 SAP2/Net	c-Fos SRE	R	Yates *et al*., 1999
GATA-1	PU.1	Light chain	R	Rekhtman *et al*., 1999 Zhang *et al*., 1999 Nerlov *et al*., 2000
GATA-2	PU.1		R	Zhang *et al*., 1999
NF-EM5(Pip)	Spi-1/PU.1	Ig L Enhancer	A	Brass *et al*., 1996 Ortiz *et al*., 1999 Perkel and Atchison, 1998 Pongubala *et al*., 1992
TFE3	Ets1/PU.1	Ig μ enhancer	A	Tian *et al*., 1999 Dang *et al*., 1998
PEBP2αB /AML1/ CBFα2	Ets1	TcRα Mo-MLV HIV-1	A A	Wooton *et al*., 1994 Giese *et al*., 1995 Sheridan *et al*., 1995 Sun *et al*., 1995 Kim *et al*., 1999
AML1	MEF	IL3	A	Mao *et al*., 1999
AML1/ETO		Promoter	R	
Tax1	Ets1	HTLV-LTR	A	Gitlin *et al*., 1993 Seeler *et al*., 1993
Tax1	Ets1	PTHr P2	A	Dittmer *et al*., 1997
Cyto megalovirus IE2	PU.1	IL-1β	A	Wara-aswapati *et al*., 1999
EBNA-3C	PU.1	LMP-1 promoter	A	Zhao and Sample *et al*., 2000
PEBP2αA/ CFBA1	Ets1	Osteopontin	A	Sato *et al*., 1998
Sp1	Ets1	PTHr P2	A	Dittmer *et al*., 1997
Pit-1/GHF-1	Ets1	PRL	A	Bradford *et al*., 1995; 1996; 1997
Pit-1β/GHF-2	Ets1		R	Bradford *et al*., 2000
Rb (unphos- phorylated)	Elf1 PU.1		R	Wang *et al*., 1993 Hagemeier *et al*., 1993
Goosecoid protein (GSC)	P.U.1		A	Konishi *et al*., 1999
CBP/p300	Ets1 Ets1/Ets2	CD13/APN MMP-1	A/R	Jayaraman *et al*., 1999 Yang *et al*., 1998
TFIID	PU.1	Basal- transcription		Hagemeier *et al*., 1993
Daxx/EAPI	Ets1		R	Li *et al*., 2000

Continued

Table 1 (*Continued*)

Partner	*Ets family*	*Target genes*	*Activity*	*References*
ubc9	Ets1			Hahn *et al*., 1997
	TEL			Chakrabarti *et al*., 1999
SMRT/	TEL		R	Chakrabarti and Nucifora *et al*., 1999
mSin3A	TEL-AML1b			Fenrick *et al*., 1999
CtBP	NET		R	Criqui-Filipe *et al*., 1999
Ets2	Ets1		A	Basuyaux *et al*., 1997
	AP-1			
ERG	Ets2 TA		R	
ERG	Ets2 ETS			
ERGp55	ERGp55			Carrere *et al*., 1998
	ERGp49			
	ERGp38			
	Fli1			
	Ets2			
	ER81			
	PU.1			
Elk1	Elk1			Drewett *et al*., 2000
GABPβ	GABPα		A	LaMarco *et al*., 1991
				Thompson *et al*., 1991
GABPγ			R	Sawada *et al*., 1994
				Suzuki *et al*., 1998
HsRPB7	EWS-FLI1		A	Peterman *et al*., 1998
TEL-PDGFR	Self	Acute	CA	Golub *et al*., 1996
beta	association	myelogenous		Jousset *et al*., 1997
		leukemia		
TEL-ABL				Papadopoulos *et al*., 1995
				Lacronique *et al*., 1997
TEL-Jak2				Ho *et al*., 1999
TEL				Peeters *et al*., 1997
				Romana *et al*., 1995
AML1	TEL/AML1		R	Hiebert *et al*., 1996

Abbreviations: A: activation or synergistic activation; R: repression; CA: constitutive activation

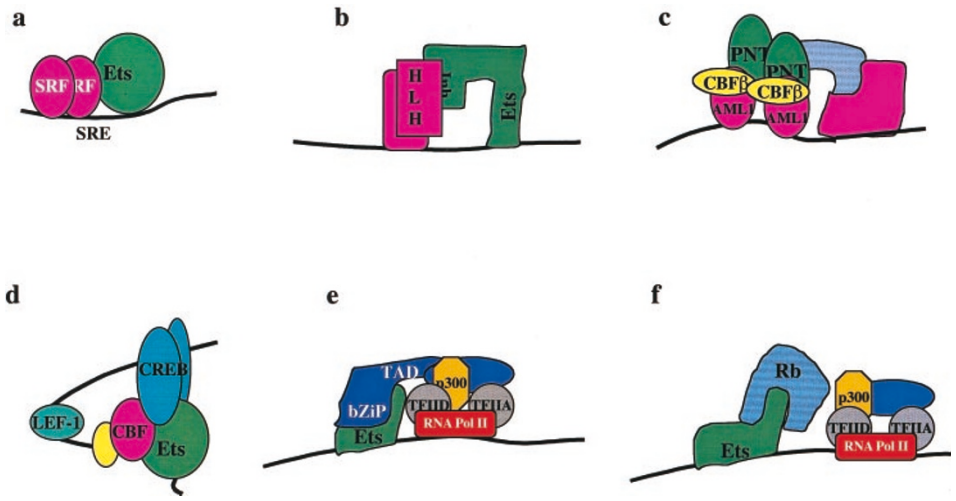

Figure 1 Summary of proposed model of Ets protein interactions with specific protein partners. (**a**) Ets act as Ternary complex factors (TCFs). ELK1 forms a ternary complex with SRF protein and the SRE motif present in the c-fos promoter (Hipskind *et al*., 1991). In most TCFs, the ETS domain is amino terminal and linked by a flexible spacer region to the SRF interaction domain (Janknecht *et al*., 1994; Ling *et al*., 1997; Shore and Sharrocks, 1994). (**b**) Intramolecular inhibition of Ets proteins can be abolished through specific protein interaction. bHLH proteins are common proteins which interact with both the inhibitory and ETS domain, resulting in removal of the intramolecular inhibition and increased DNA binding ability of Ets protein, respectively (Maira *et al*., 1996; Petersen *et al*., 1995; Tian *et al*., 1999). (**c**) The Pointed domain is found in a subset Ets family members and mediates protein-protein interaction between Ets family members allowing formation of homo- or hetero-dimers. This dimerization may block transcription or allow constitutive signalling (Fears *et al*., 1997; Hiebert *et al*., 1996; Jousset *et al*., 1997). (**d**) The stable interaction between two proteins having distal DNA binding sites (Ets1 and CREB) requires a third protein (CBF). Structural alterations, such as the DNA bending via LEF1, can further stabilize macromolecular complexes, leading to synergistic activation on enhancer TCRα (Giese *et al*., 1995; Mayall *et al*., 1997) and HIV-1 (Sheridan *et al*., 1995). (**e**) Protein-tethered transactivation (PTT). Transcription factors may function in genes that do not have the required DNA binding site in the promoter region. Binding of one transcription factor serves as a tether for another transcription factor. (Behre *et al*., 1999; Wara-aswapati *et al*., 1999; Yang *et al*., 2000; Zhao and Sample, 2000). (**f**) Ets interacting partner may bridge or block the cooperation between an Ets factor and the basal transcriptional machinery (Jayaraman *et al*., 1999; Yang *et al*., 1998)

signals (Yates *et al*., 1999). Similarly, ERF (Ets2 Repressor Factor) can disrupt the cooperative interactions between Pit-1 and Ets1, blocking Pit-1-dependent prolactin promoter activity in response to cAMP signals (Day *et al*., 1998).

Hetero- or homo-dimerization

Most of Ets protein bind to DNA as monomer. The only example of Ets protein binding to DNA as a hetero-dimer is the transcription factor GA-binding protein (GABP$\alpha\beta$) (LaMarco *et al*., 1991; Thompson *et al*., 1991). GABP$\alpha\beta$ is composed of two subunits, GABPα and GABPβ. GABPα, contains the ETS domain and GABPβ contains the transactivation domain (TAD) and the ankyrin repeats (Brown and McKnight, 1992; LaMarco *et al*., 1991; Thompson *et al*., 1991). The transcriptional activity of GABPα is dependent upon its heterodimerization with GABPβ and the DNA binding affinity of GABPα can be greatly enhanced by this heterodimerization (Gugneja *et al*., 1995). However, the heterodimer of GABPα with GABPγ is unable to active transcription even though GABPγ is able to enhance GABPα DNA binding (Sawada *et al*., 1994; Suzuki *et al*., 1998). The ratio of GABPβ to GABPγ may thus control GABP hetero-dimer-dependent transcription in a tissue specific manner (Suzuki *et al*., 1998). Homo-dimerization within the Ets family involves the Pointed/HLH domain. The Pointed domain, the second conserved domain in a subset of Ets family proteins, possesses an independent structure with unique architecture of a monomeric five-helix bundle (Slupsky *et al*., 1998). The dimerization via Pointed domain of aberrant fusion proteins lead to a permanent signal activity in signaling transduction, which are characteristic of the leukemic cells (Ghysdael and Boureux, 1997; Golub *et al*., 1994; 1996; Ho *et al*., 1999; Jousset *et al*., 1997; Lacronique *et al*., 1997; Papadopoulos *et al*., 1995; Peeters *et al*., 1997; Romana *et al*., 1995). The isoforms of ERG, a Pointed domain containing Ets family member, form homodimers with itself or hetero-dimers with some other Ets proteins including Fli-1, Ets2, Er81 and PU.1 via Pointed domain and/or ETS domain (Carrere *et al*., 1998). Recently, Drewett and his colleague have shown that the formation of inducible dimerization of Elk-1 may be the mechanism by which the MAP kinase signal are transferred to the transcriptional control (Drewett *et al*., 2000).

Protein turnover

Ets proteins are in general characterized as relatively unstable proteins. The half-life of Ets2 is only 20 min (Fujiwara *et al*., 1988). Although the mechanism leading to Ets degradation is not yet characterized, it has been previously demonstrated that Ets1 interacts with Ubc9, an ubiquitin-conjugating enzyme. However, Ets1 stability does not seem to be affected by over-expression of the Ubc9 gene in cells; indeed, co-transfection of Ubc9 with Ets1 in mammalian cells increases the transcription activity of Ets1 (Hahn *et al*., 1997). Ubc9 also has been shown to physically interact with TEL (Chakrabarti *et al*., 1999) and Ets1 (Hahn *et al*., 1997; Li *et al*., 2000) through the HLH/Pointed domain. However, it seems that the effect of Ubc9 on Ets transcription activity is not mediated by degrading its target protein. Recently, we have identified an interaction between Ets1 and Uba2 (Li *et al*., unpublished data), which has been shown to target proteins for uniquitinization and degradation by SUMO-1 (Dohmen *et al*., 1995; Okuma *et al*., 1999). Further experiments will be required to determine whether Uba2 plays a role in turn-over of Ets1.

Future directions

To date, all the known functional domains of Ets proteins are also associated with interactive protein partners. However, the biological significance of many of these interactions need to be further evaluated (Table 1, Figure 1). It is clear that the Ets family plays an important role in control of physiological condition, development process and neoplastic biological processes. Overlap between specific protein–protein interactions may provide a mechanism to control the diverse functions of Ets family. Such combinatorial control provides a mechanism to fine-tune the networks of cellular processes. As an end effector of signaling tranduction pathway, it is critical to determine how extracellular signals are transduced into transcriptional activity (Yordy and Muise-Helmericks, this issue). Future studies will define the precise interactions between Ets proteins, basal transcriptional machinery, co-repressors or co-activators and other bridging proteins that collectively are critical for transcriptional responses. Efforts are needed to continue precise characterization of Ets protein–partner associations and to determine how these interactions influence target gene selection and transcription activation or repression. It is important to correlate specific physical interactions with physiological processes. More sensitive methods need to be developed to allow characterization of transient interactions and for direct assessment of the biological consequences of specific interactions. Crystallographic determination of the structure of multiple protein complexes will help in understanding the combinatorial control of transcription. Ultimately, the protein–protein interface may provide a unique target for intervention. Thus, providing a novel approach for blocking aberrant signaling pathways or reversing the malignant phenotype associated with oncogenic transcription factors.

Acknowledgments
This work was supported in part by National Institutes of Health Grants P01CA78582 to DK Watson and American Cancer Society Grant IRG97-151 to R Li. This article is dedicated to the memory of Dr Takis S Papas, a mentor, scientific colleague and friend.

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