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Ets target genes: past, present and future

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Ets is a family of transcription factors present in species ranging from sponges to human. All family members contain an approximately 85 amino acid DNA binding domain, designated the Ets domain. Ets proteins bind to specific purine-rich DNA sequences with a core motif of GGAA/T, and transcriptionally regulate a number of viral and cellular genes. Thus, Ets proteins are an important family of transcription factors that control the expression of genes that are critical for several biological processes, including cellular proliferation, differentiation, development, transformation, and apoptosis. Here, we tabulate genes that are regulated by Ets factors and describe past, present and future strategies for the identification and validation of Ets target genes. Through definition of authentic target genes, we will begin to understand the mechanisms by which Ets factors control normal and abnormal cellular processes. *Oncogene* (2000) **19,** 6533–6548.

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Introduction

Regulation of gene expression is controlled through the combinatorial action of multiple transcription factors, which function to activate or repress transcription via binding to *cis*-regulatory elements present in target genes. Identification of functional target gene promoters that are regulated by specific transcription factors is critical for initiating studies to increase understanding of the molecular mechanisms that control transcription. Furthermore, identification of target gene promoters for normal and oncogenic transcription factors provides insight into the regulation of genes that are involved in control of normal cell growth, and differentiation, as well as provide information critical to understanding cancer development.

It has been over 15 years since Ets was originally identified as one of the two genes (Ets and Myb) transduced by the avian leukemia virus, E26 (Watson *et al*., 1990); (Reviewed in this issue by Blair and Athanasiou). Since the cloning of the v-ets gene, over 30 Ets domain-containing genes have been identified, either by sequence homology or as sites of viral integration and activation. Ets genes have been characterized in species ranging from sponges, nematodes and insects to humans. The Ets family proteins are transcription factors containing a winged helix-turn-helix DNA binding domain. (Reviewed (Ghysdael and Boureux, 1997; Graves and Petersen, 1998; Watson, 2001)). All Ets transcription factors bind to unique GGAA/T DNA sequences (EBS, Ets Binding Sites). Such EBS have been identified in the promoter/enhancer regions of viral and cellular genes, and thus control the expression of genes critical for the proper control of cellular proliferation, differentiation, development, hematopoiesis, apoptosis, metastasis, tissue remodeling, angiogenesis and transformation. Our current literature survey allowed identification of over 200 Ets target genes, and the number of genes shown to be regulated via EBS is constantly increasing. This number of Ets target genes is between those previously estimated for p53 (estimated between 200–300 target genes, (Tokino *et al*., 1994)) and for the hormone receptor family (50–100 genes; (Evans, 1988)). Further establishing the importance of Ets factors, a recent study demonstrated that EBS were among the eight most important DNA motifs in minimal responsive synthetic promoters generated using random oligonucleotides (Edelman *et al*., 2000). In addition to their importance in normal cellular control, based upon predominance of target genes, Ets products have also been implicated in several malignant and genetic disorders. For example, the human Ets genes, FLI1, TEL and ERG, are located at the translocation breakpoints of several leukemias and solid tumors, forming chimeric proteins believed to be responsible for tumorigenesis (Dittmer and Nordheim, 1998); (Mavrothalassitis and Ghysdael, Truong and Ben-David, in this issue). In addition, Ets factors have been found to be overexpressed (e.g., Ets2 in prostate and breast cancer (Sapi *et al*., 1998; Sementchenko *et al*., 1998)) or lost (e.g. PSE in prostate cancer (Nozawa *et al*., 2000)) during cancer development. Most of the target genes that mediate phenotypes associated with dysregulated expression remain to be defined.

The importance of the Ets family of transcription factors in various biological and pathological processes necessitates the identification of downstream cellular target genes of specific Ets proteins. Although some overlap in the biological function of different Ets proteins may exist, the emergence of a family of closely related transcription factors suggests that individual Ets members may have evolved unique roles, manifested through the control of specific target genes. Several key areas are critical for understanding what defines a functionally important Ets target gene: First, the functional importance of the EBS must be demonstrated by mutagenesis. Second, the Ets factor or factors responsible for transcriptional control of specific target genes need to be identified. While

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extensive publications have identified functionally important Ets binding sites (EBS) and thus, Ets target genes (Table 1), relatively few investigations have identified definitive target genes for a specific Ets factor. Third, it is becoming increasingly evident that cellular context defines the direction and magnitude of response to Ets factors. Indeed, future efforts will lead to discovery of the co-factors that modulate transcriptional regulation by Ets factors. Collectively, we are beginning to define the molecular mechanisms that determine which Ets family member will regulate a particular target gene and are developing appropriate approaches to determine which target genes are necessary for Ets-dependent phenotypes.

Ets target genes: the past

Initially, identification of Ets targets was based upon the presence of the GGAA/T core sequences in the promoters/enhancers of various cellular or viral regulatory regions. Subsequently, synthetic oligonucleotides containing presumptive Ets binding sites (EBS) have been used in electrophoretic mobility shift assays (EMSAs) with proteins prepared as nuclear extracts or by *in vitro* transcription/translation of specific Ets factor cDNAs. Competition using excess oligonucleotide or with oligonucleotides containing mutations in the presumptive EBS are tests for specificity. The Ets factor(s) responsible for specific DNA-protein complexes has been identified by antibody inhibition/supershift analyses. Transient transfection with native promoter–reporter genes or reporters containing the minimal promoter linked to the putative Ets binding sites are often used to demonstrate transcriptional activation or repression via Ets factors. The functional importance of specific sequences can be further analysed using deletions of various regions in the promoter sequence. The importance of particular candidate EBS can thus be demonstrated by mutagenesis. Table 1 provides a list of Ets target genes that have been identified using these approaches. Collectively, functional Ets sites have been characterized in viral genes and cellular genes encoding transcription factors, transforming and tumor-associated products, proteinases, cell cycle and apoptosis regulators, signaling molecules, receptors and other cell surface molecules, ligands and tissue specific products.

Ets target genes: the present

The consensus binding sites for several Ets factors have been determined by enrichment of high affinity oligonucleotides from pools of oligonucleotides with random sequences. Such analyses have demonstrated that Ets family members often differ in their exact binding site preference outside of the GGAA/T core, with factor-specific recognition spanning nine to 15 base pairs (Ghysdael and Boureux, 1997; Graves and Petersen, 1998). However, in the last several years it has become apparent that Ets factors are able to bind to sites that do not conform to their *in vitro* derived high affinity consensus sequences. For example, the J-chain transcription factor NF-JB was purified by DNA affinity chromatography using sequences derived from the J-chain promoter and was subsequently found to be identical to PU.1. Significantly, the NF-JB site does not contain what had been previously felt to be an invariant GGA core sequence, but rather A<u>AGAA</u>A (Shin and Koshland, 1993). PU.1 has subsequently been found to bind to other sequences lacking the GGA core, including Macrophage scavenger receptor (AG<u>AGAA</u>GT, (Moulton *et al*., 1994)) and IL-1β (GC<u>AGAA</u>GT (Buras *et al*., 1995; Kominato *et al*., 1995)). Target gene specificity and affinity of Ets factors to EBS is ultimately controlled by the precise sequence context/geometry of the EBS in relation to other *cis*-elements. The importance of neighboring elements for maximizing function via EBS is explained in part by the ability of Ets factors to form complexes and act synergistically with members of other transcription factor families. One example of co-dependence between Ets and other transcription factors is the synergistic binding and cooperative activation via Ets1, CREB and AML1 non-consensus binding sites in the human T-cell receptor beta chain promoter. Furthermore, it has been suggested that such low-affinity sites mediate cooperative concentration-dependent promoter regulation, while high-affinity sites may be associated with constitutive activation (Halle *et al*., 1997). Unique combinations of protein–protein interactions are likely to direct different Ets factors to regulate the expression of specific target genes. It is this precise assembly of multiple transcription factors onto a chromatin template that enhances transcriptional specificity and defines activation or repression function. (For further discussion, see review by Li *et al*., in this issue).

A subset of Ets factors have repressor activity (e.g. ERF, YAN, TEL, NET) and may directly compete with other Ets factors for binding to EBS sites (Table 1, e.g. MMP-3/TEL, M-CSF/TEL, Prolactin/ERF and Rb/Fli1). In addition, interaction with other proteins can block the ability of Ets factors to activate transcription (See article by Mavrothalassitis and Ghysdael, in this issue). The ability of individual Ets factors to function as activators or repressors is also dependent upon promoter and cell context. For example, studies using dermal fibroblasts indicate that Fli1 can function as an activator for the TN-C promoter, while acting as a repressor in the context of the collagen promoter. Ets1, on the other hand, activates both promoters (Shirasaki *et al*., 1999; Czuwara-Ladykowska *et al*., submitted; Trojanowska, in this issue). Furthermore, Fli1 has been shown to act as a repressor of Rb (Tamir *et al*., 1999). Unique promoter interactions with specific Ets factors have also been demonstrated in the case of Ets2 (or Ets1) and Erg on the collagenase (MMP1) and stromelysin (MMP3) promoters. Erg appears to act as an activator of the collagenase promoter, while it inhibited stimulation of stromelysin promoter by Ets2, whereas Ets2 stimulated both (Buttice *et al*., 1996). Recruitment of CBP/p300 by Ets2 seems to play an important role in activation of the stromelysin promoter (Jayaraman *et al*., 1999). Importantly, Erg was not able to cooperate with CBP/p300 in the context of this promoter, which may explain differential effects of Ets2 and Erg on the activity of this promoter.

Successful identification of target genes controlled by one (or more) Ets factors will require the use of

Table 1 Ets target genes

Promoter	*Tissue/Cell line*	*ETS gene*	*EBS*	*Assay*	*References*
		Viral genes			
CMV immediate early promoters	U937 HL-60	Elk1	GAGTTCCGCT	m,e	(Chan *et al*., 1996)
EBV NA2	Raji	PU.1	AGGGGAAGTA	m	(Laux *et al*., 1994)
E4 (adenovirus early promoter)	SL2	GABP	AACGGAAGTG	e,t	(Sawada *et al*., 1999)
EIAV (Equine Infectious anemia virus)	Monocytes HeLa	PU.1	AACTTCCTGT	m,d	(Carvalho and Derse, 1993; Maury, 1994)
MMLV	EL4.E1 (murine T-cell) NIH3T3 Ti-6	Ets1, GABP	ACAGGATATC	m, ivf	(Granger and Fan, 1998; Gunther and Graves, 1994)
Polymerase (HIV-1)	U937, CEM	PU.1	MS	m,e,f	(Van Lint *et al*., 1994)
HTLV-1 LTR	HeLa SL2	Ets1	MS	d	(Bosselut *et al*., 1990; Gegonne *et al*., 1993; Gitlin *et al*., 1991)
HIV-2 LTR enhancer	HL-60, U937, KG-1, THP-1 Jurkat	Elf1, PU.1	MS	m	(Hilfinger *et al*., 1993; Leiden *et al*., 1992; Markovitz *et al*., 1992)
HIV-1 LTR	Jurkat, Molt 4	Ets1	TGCATCCGGA	m,e	(Holzmeister *et al*., 1993; Sieweke *et al*., 1998)
HTLV-1 enhancer LTR	Jurkat	Elf-1	MS	d,m	(Clark *et al*., 1993; Tanimura *et al*., 1993)
c-mil (avian retrovirus MH2)	Chicken embryo fibroblasts	EBS	CTCTTCCTCG GGAGGAAGGA	d	(Ansieau *et al*., 1993)
Polyomavirus mutant	PCC4 Embryonic carcinoma	EBS	MS	d	(Nothias *et al*., 1993)
Lentivirus	HeLa	PU.1	AACTTCCTGT	e,m	(Carvalho and Derse, 1993)
Latent Membrane Protein 1 (EBV)	BJAB (Burkitt lymphoma)	PU.1	TACTTCCCCT	d	(Johannsen *et al*., 1995)
		Transcription factors			
Hoxb-3	Mouse embryo	EBS	GTGTTCCTCC	e,f	(Manzanares *et al*., 1997)
p53	COS	Ets1, Ets2	TACGGAAAGCCTT TTA	m, meth	(Vananzoni *et al*., 1996)
N-myc2	HepG2, Woodchuck liver tumors/Huh7 (hepatoma)	Ets1, Ets2, PEA3	AGCGGAAAAG AAGGGAAGCA	d,m	(Flajolet *et al*., 1997)
c-myb	Molt-4-ML-1 (myeloblastic leukemia)	Ets	GAAGGAAAAA TCAGGAAAAG	m, meth	(Sullivan *et al*., 1997; Wang *et al*., 1994b)
TBP (TATA binding protein)	HeLa, Nam	EBS	GCCGGAAGTG	d,m	(Foulds and Hawley, 1997)
GATA-1	Cos, HeLa	Ets1, Ets2, Fli1	ACAGGAAGGA	m	(Aurigemma *et al*., 1992; Seth *et al*., 1993)
c-fos	HeLa	EBS	GCAGGATGTT	e	(Liu and Ng, 1994)
TFEC (macrophage specific leu Zipper)	NIH3T3 RAW 264.7	Ets2, PU.1	MS	e	(Rehli *et al*., 1999)
JunB	P19 EC, HepG2 Bal 17 (mature B-cell, murine)	Ets1, Ets2	ACAGGAAGCG	d,m	(Amato *et al*., 1996; Coffer *et al*., 1994; Fujitani *et al*., 1994; Nakajima *et al*., 1993)
AML1	HEK, Jurkat	EBS	AATGGAATTT	d,m	(Ghozi *et al*., 1996)
PU.1	U937, Mono Mac6, M1	PU.1, Spi-B	TCAGGAACTT	d,m	(Chen *et al*., 1995; Kistler *et al*., 1995)
Fli1	745-A	PU.1	ACCTTCCTCC CACTTCCCAA	d,m	(Starck *et al*., 1999)
ERF	HeLa	EBS	TCCTTCCTCC	d	(Liu *et al*., 1997)
NF-κB1	Jurkat	Ets1	CCAGGAAGTG	m,e	(Lambert *et al*., 1997)
Egr-1	NIH3T3, mononuclear phagocytes *Xenopus* Embryo	Ets1, Fli1	GGCTTCCTGC	d	(Panitz *et al*., 1998; Robinson *et al*., 1997; Yan *et al*., 1999)
RANTES	Primary Monocytes, MM6	PU.1	AGAGGAAACT	d,m	(Boehlk *et al*., 2000)
FREAC winged helix TF (kidney)	COS-7, 293	Ets1	MS	d,m	(Cederberg *et al*., 1999)
		Transforming/tumor associated genes			
GnT-V(N-Acetylglucosaminyl-transferase V) metastasis	HuCC human bile duct carcinoma HepG2, Kato-III	Ets1	TGAGGATGAT AGAGGAACTT	d,m	(Kang *et al*., 1996; Ko *et al*., 1999)
Urokinase type plasminogen activator	HeLa, HepG2, NIH3T3, HT 1080, U251(glioma), Sk-Br-3	Ets2, Ets1,	GGAGGAAATG	d,m	(Besser *et al*., 1995; Kondoh *et al*., 1998; Nakada *et al*., 1999; Nerlov *et al*., 1991; Ried *et al*., 1999; Rorth *et al*., 1990; Stacey *et al*., 1995; Watabe *et al*., 1998)

Continued

Table 1 (*Continued*)

Promoter	*Tissue/Cell line*	*ETS gene*	*EBS*	*Assay*	*References*
Mage-1	MZ2-MEL	EBS	CCCGGATGTG	d, m, meth	(De Smet *et al*., 1995; 1996)
		Proteinases/inhibitors			
MMP-1 (Collagenase 1)	HepG2	Erg, Ets2	AGAGGATGTT	m	(Buttice *et al*., 1996; Chapman *et al*., 1999; Gutman and Wasylyk, 1990)
MMP-3 (Stromelysin 1)	HepG2, HeLa	Erg, Ets1, Ets2 Repression by TEL	CCAGGAAGTG	d,m	(Buttice *et al*., 1996; Buttice and Kurkinen, 1993; Fenrick *et al*., 2000; Jayaraman *et al*., 1999; Wasylyk *et al*., 1991)
MMP-9 (Collagenase IV)	MG63 (osteosarcoma), HT1080, MCF7	E1AF, Ets2, Ets1	MS	d	(Gum *et al*., 1996; Higashino *et al*., 1995; Himelstein *et al*., 1997; Kaya *et al*., 1996; Munaut *et al*., 1999; Turque *et al*., 1997; Watabe *et al*., 1998)
Cathepsin B	U87 (glioma)	EBS	MS	d	(Yan *et al*., 2000)
Neutrophil Elastase and proteinase 3 (immature myeloid cells)	32Dcl3 (murine myeloid cell line)	PU.1, GABP	GGAGGAAGTA	d,m	(Nuchprayoon *et al*., 1994, 1997, 1999; Oelgeschläger *et al*., 1996)
Maspin	70N (normal mammary epith), MDA231, LNCap, CF3	EBS	AACTTCCTGC CCCTTCCTGC	d	(Zhang *et al*., 1997b,c)
TIMP-1	F9 (embryonic carcinoma)	Ets1	CCAGGAAGCC	d	(Botelho *et al*., 1998; Logan *et al*., 1996)
		Cell cycle regulation genes			
CDC2	NIH3T3	Ets2	CCGGGAAGGC	m, ivf	(Tommasi and Pfeifer, 1995; Wen *et al*., 1995)
Cyclin D1	JEG-3 (trophoblast), COS	Ets2	CATGGAACAC	d,t	(Albanese *et al*., 1995)
Rb	HEL, C33A	GABP Repression by Fli1	GGCGGAAGTC	m,e	(Savoysky *et al*., 1994; Tamir *et al*., 1999)
p21 (Waf1/Cip1)	SiHa, MCT, HepG2	E1AF, Ets2	CAGGGAACAT	d,m	(Beier *et al*., 1999; Funaoka *et al*., 1997; Park *et al*., 2000)
		Apoptosis-related genes			
Bcl-2	Ts21, transformed myeloblasts	Myb-Ets	MS	t	(Frampton *et al*., 1996)
Bcl-X_L	293	Ets2	MS	d	(Sevilla *et al*., 1999)
MCL1 (Bcl family member)	ML-1 (human myeloblasts)	EBS	TCCGGAAGCT	d, m	(Townsend *et al*., 1999)
Fas (CD 95)	Jurkat	GABP	CCAGGAAATA ACAGGAAGTA	d,m	(Li *et al*., 1999c)
PARP	EWS	EBS	MS	d	(Soldatenkov *et al*., 1999)
		Cell signaling			
c-fes (myeloid-specific tyr kinase)	K562, U937	PU.1	GGAGGAAGCG	d,m	(Heydemann *et al*., 1996; Ray-Gallet *et al*., 1995)
Btk (tyrosine kinase agammaglobulinemia)	K562, DG 751	PU.1	AAGGGAACTG	m	(Müller *et al*., 1996)
PK CK2α (casein kinase II)	HeLa	EBS	GGTTTCCGCT	d,m	(Krehan *et al*., 2000)
PKC-η	HaCaT (human keratinocyte)	EBS	GAAGGAAGAA GAGGGAAGGA	d,m	(Quan and Fisher, 1999)
Lck type 1	Jurkat, HeLa	EBS	GCAGGAAGTG	d, m	(Leung *et al*., 1993; McCracken *et al*., 1994)
Btk ptk (XLA)	DG75, K562	EBS	TCAGGAAACA	t	(Sideras *et al*., 1994)
		Cellular receptors and antigens			
Fc ε RI α chain (IgE receptor)	PT18 (murine mast), RBL-2H3	Elf-1	CATTTCCTTC	d,m	(Nishiyama *et al*., 1999)
FcγR1	RAW264.7, HeLa U937, THP1, HL60	PU.1	AAAGGAACGT TCCTTCCTCT	d,m	(Eichbaum *et al*., 1994; Perez *et al*., 1994)
FcγRIIIa	RAW264.7	PU.1	TCCTTCCTCT	d,m	(Feinman *et al*., 1994)
M-CSF-R1 (c-fms)	Aortic median smooth muscle cells, RAW 264, NIH3T3, Cos	Ets1, Ets2, PU.1 Repression by TEL	AGGGGAAGAA	d,m	(Fears *et al*., 1997; Inaba *et al*., 1996; Reddy *et al*., 1994; Ross *et al*., 1998; Zhang *et al*., 1994, 1996)
GM-CSF-R	U937	PU.1	TGAGGAAGCA	d,m	(Hohaus *et al*., 1995)
γc chain (subunit of IL R)	Raji, Jurkat	EBS	ACCGGAAGCT AGAGGAAACG	d,m	(Markiewicz *et al*., 1996)
TCR α	Jurkat	Ets1	CACATCCTCT	f,t	(Ho *et al*., 1990; Mayall *et al*., 1997)
TCR β	Jurkat	Ets1	ACAGGATGTG	d,m	(Halle *et al*., 1997; Wotton *et al*., 1993)

Continued

Table 1 (*Continued*)

Promoter	*Tissue/Cell line*	*ETS gene*	*EBS*	*Assay*	*References*
TCR ξ	Jurkat	Elf-1	CACTTCCTGG GGCTTCCTGC	d	(Rellahan *et al*., 1998)
TCR Vδ1	T245 (murine T cell), T245/BW (hybridoma)	EBS	TGAGGAAGTG	d,e	(Kienker *et al*., 1998; Punturieri *et al*., 1993)
IL-2R α	PC60 (rodent T-lymphoma derived), Jurkat	Elf-1	TCAGGAAGTT	m,ivf	(John *et al*., 1995; Serdobova *et al*., 1997)
IL-2R β	Jurkat, Kit-225	Ets1, GABP	ACAGGAAGTG	d,m	(Lin *et al*., 1993b)
IL-2R γ	Jurkat, THP-1	EBS	MS	d	(Ohbo *et al*., 1995)
IL-3R α	PT18 (murine mast cell)	EBS	TCAGGAAGTT	d	(Miyajima *et al*., 1995)
IL-3/IL-5/GM-CSF β R subunit	U937, HL-60	PU.1	TGCTTCCTCT TGTTTCCTGA	m,d	(van Dijk *et al*., 1998)
CXCR1 (IL-8 receptor)	RAW, 23D	PU.1	TATTTCCGTT	d	(Wilkinson and Navarro, 1999)
P2Y10, lymphoid restricted heptahelical receptor	MEL, EL-4, A20	PU.1, Spi-B	TACTTCCTCT	m	(Rao *et al*., 1999)
Mannose receptor	NR 8383 (macrophage)	PU.1	MS	d,m	(Egan *et al*., 1999)
Macrophage scavenger receptor	THP-1	PU.1	AAGAGAAGTG	m	(Moulton *et al*., 1994)
MPL	HEL, K562	EBS	MS	m	(Alexander and Dunn, 1995; Deveaux *et al*., 1996)
Kit	K562	EBS	MS	d,m	(Ratajczak *et al*., 1998)
Tissue Factor (receptor for factor VII/VIIa)	THP-1	EBS	AGTTTCCTAC CCTTTCCTGC	e,t	(Donovan-Peluso *et al*., 1994)
HER2/neu	MFC-7, MDA-453	ESX	TGAGGAAGTA	d,m	(Chiang *et al*., 2000; Scott *et al*., 1994)
Met/HGFR	MLP (Murine liver progenitors)	Ets1	GGAGGAAGCG	m	(Gambarotta *et al*., 1996)
TGF-β TypeIIR	HepG2	ERT	AGTTTCCTGT	d	(Choi *et al*., 1998)
N-Acetylcholine Receptor ε δ subunits	Primary rat muscle, chick myotubes	GABP, Ets2	CCCGGAACTG CGTTTCCGGC	d,m	(Sapru *et al*., 1998; Schaeffer *et al*., 1998
		Cytokines, Growth Factors, Ligands			
Factor IX	HepG2	GABP	CACTTCCTGT	m,e	(Boccia *et al*., 1996)
Lymphotoxin-β (TNF-β)	Jurkat	EBS	ACAGGAAGCT	m	(Kuprash *et al*., 1996; Pokholok *et al*., 1995)
GM-CSF	MLA 144 (T-cells), Jurkat	Elf-1, Ets1	MS	m	(Coles *et al*., 2000; McKinlay *et al*., 1998; Nimer *et al*., 1996b; Thomas *et al*., 1995, 1997; Wang *et al*., 1994a)
TF (tissue factor)	THP-1	Ets1, Ets2	GCAGGAAGTG	f,e	(Groupp and Donovan-Peluso, 1996)
PDGF	JEG-3	EBS	GCCGGATGAC	d,m	(Maul *et al*., 1998)
TPO	PLC, HepG2	GABP/E4TF	CACTTCCGGG	d,m	(Kamura *et al*., 1997)
IL-1β	HeLa, RAW	PU.1	AGCAGAAGTA	d,m	(Buras *et al*., 1995; Kominato *et al*., 1995; Yang *et al*., 2000)
IL-2	Jurkat	GABP, Elf-1	MS	d,m	(Avots *et al*., 1997; Hoffmeyer *et al*., 1998; Thompson *et al*., 1992)
IL-3	CMK	EBS	CATGGATGAA	m	(Nimer *et al*., 1996a)
IL-4	ABFTL-3 (mast cell)	PU.1	CAGTTCCTGC	m	(Henkel and Brown, 1994)
IL-5	Jurkat, Kasumi	Ets1, Ets2	CATTTCCTCA	m	(Blumenthal *et al*., 1999)
IL-12	RAW, RPMI-8866 (EBV-tr. lymphoblastoid cell)	PU.1, Ets2	CATTTCCTCT	d	(Gri *et al*., 1998; Ma *et al*., 1997)
IL-1R antagonist	RAW, HT1080	PU.1	TATTTCCGCT	d,m	(Smith *et al*., 1998)
MCP-3	MG-63	EBS-Repressor	GTCTTCCTCT	d	(Murakami *et al*., 1997)
LIF (leukocyte inhibitory factor)	Jurkat	EBS	MS	d	(Bamberger *et al*., 1997)
Prolactin	HeLa, Cos, GH_4T2 (rat pituitary tumor)	Ets1 Repression by ERF	AAAGGAAAAC	d,m	(Bradford *et al*., 1995, 1997; Castillo *et al*., 1998; Howard and Maurer, 1995) (Day *et al*., 1998)
Somatostatin	HeLa, GH4	Elk-1	MS	d,m	(Jacob *et al*., 1995)
PTHrP (Hypercalcemia of malignancy)	Jurkat, Schneider	Ets1	TCCGGAAGCA	d,m	(Dittmer *et al*., 1993, 1994, 1997)
Interferon-γ	RAW264.7	PU.1, Spi-B	GATGGAAGTT GCCTTCCCGT	d,m	(Nguyen and Benveniste, 2000)
Interferon-τ	Jar (choriocarcinoma)	Ets2	CCAGGAAGTG	m	(Ezashi *et al*., 1998)
TNF-α	Jurkat, HuT78, J774, THP-1	Ets1, Elk-1, PU.1	MS	m	(Kramer *et al*., 1995; Steer *et al*., 2000; Tsai *et al*., 2000)
FGF-1	NIH3T3	EBS	TGGGGATGTG	m	(Chotani *et al*., 2000)

Continued

Table 1 (*Continued*)

Promoter	*Tissue/Cell line*	*ETS gene*	*EBS*	*Assay*	*References*
FGF-BP	ME-180 (squamous cell carcinoma)	EBS	GGAGGAGCTG	d	(Harris *et al*., 1998)
		Cell surface molecules			
E-Cadherin	MCA3D	EBS-repressor	CAGTTCCTTG	d,m, ivf	(Rodrigo *et al*., 1999)
α4 Integrin	Jurkat	EBS	GGAGGAAGGA GAAGGAAGTG	d	(Postigo *et al*., 1997; Rosen *et al*., 1994)
β4 Integrin	DAB1	EBS	CCTTTCCGGG	d,m	(Takaoka *et al*., 1998)
α_v Integrin	HeLa, B16F10	EBS	CACTTCCTCC CACGGAAGTC	d,m	(Donahue *et al*., 1994; Kambe *et al*., 1998; Tajima *et al*., 2000)
I-CAM1 (CD 54)	EAhy926 (hybrid of HUVEC and A549)	EBS	AGTTTCCCAG	d,m	(Roebuck *et al*., 1995)
LW	K562, HeLa	EBS	CCCTTCCTCT	t	(Hermand *et al*., 1996)
Rh associated GP	K562, HEL	EBS	CAATTCCAAC	m	(Iwamoto *et al*., 2000)
CD4	Jurkat, CEM	EBS	GGGTTCCTGT	m	(Rushton *et al*., 1997; Slamon *et al*., 1993)
CD5	Primary spleen cells	EBS	GACTTCCTCT	d,m	(Berland and Wortis, 1998)
CD8α	Jurkat, JM	EBS	CACATCCTCC	m	(Hambor *et al*., 1993)
CD11a (leukocyte integrin)	CEM, U937	EBS	CACTTCCTCC	d	(Noti *et al*., 1996; Shelley *et al*., 1993)
CD11b	THP-1, U937	PU.1	MS	d,m, ivf	(Chen *et al*., 1993; Hickstein *et al*., 1992; Pahl *et al*., 1993)
CD13 (aminopeptidase N)	KG1a (myeloblastic)	EBS	MS	d,m	(Olsen *et al*., 1997; Shapiro, 1995; Yang *et al*., 1998a)
CD18(+CD11=β_2 leukocyte integrin)	U937, CEM	GABP, PU.1	ACAGGAAGTG CACTTCCTCC	m	(Bottinger *et al*., 1994; Rosmarin *et al*., 1995a,b, 1998)
CD34	Tk-ts13 hamster fibroblasts	Ets2	CGAGGAAAAA	m	(Melotti and Calabretta, 1994)
CD72	M12.4.1 (B-lymphoma)	PU.1	TTCTTCCTCT	d	(Ying *et al*., 1998)
Presenilin-1	HepG2	EBS	GCCGGAAATG	d,m	(Pastorcic and Das, 1999)
Utrophin	C2, L6	GABP	ATCTTCCGGAA CAA	t,e	(Gramolini *et al*., 1999; Khurana *et al*., 1999)
		Lymphoid/myeloid specific			
HLA-DRA	Raji	Ets1	CCCTTCCCCT	m	(Jabrane-Ferrat and Peterlin, 1994)
MIP-1α, Macrophage Inflammatory protein 1α	RAW264.7, MEL	PU.1	MS	e,f	(Grove and Plumb, 1993)
Platelet Basic Protein	HEL	PU.1	CACTTCCTCC	d,m	(Zhang *et al*., 1997a)
GP Ibα	HEL	EBS	AAAGGAAAGC	d,m	(Hashimoto and Ware, 1995)
GP IIb	HEL, K562, U937, UT7	EBS	MS	d,m	(Block *et al*., 1996; Doubeikovski *et al*., 1997; Prandini *et al*., 1996)
GP V	HEL, Dami, K562, HL60	EBS	TCAGGATGCA	d	(Lepage *et al*., 1999)
GP IX	293T, HEL	Fli1, GABP, PU.1	CACTTCCTTC	d,m	(Bastian *et al*., 1996, 1999; Hickey and Roth, 1993)
Von Willebrand Factor	HUVEC, CPAE	EBS	CATTTCCTTT TGTTTCCTTT	m	(Schwachtgen *et al*., 1997)
Platelet factor 4	HEL, MEG-01	Ets1	ACCGGAAGTCGGG AAGGC	m	(Minami *et al*., 1998)
B29 (B-cell)	729(B-lb)	EBS	GCAGGAAGGG TGAGGAAGAG	e,t	(Thompson *et al*., 1996)
mb-1	B-cell	EBS	MS	d	(Leduc and Cogne, 1996)
L-plastin (actin binding) – leukocytes	K562, P388D1, HuT-14	EBS	AGAGGAAGTG	d,f	(Lin *et al*., 1993a, 1997)
IgE-GLP (germline promoter)	DG75	PU.1	AAGGGAACTT	d,m	(Stutz and Woisetschlager, 1999)
IgH enhancer	U-937 (human monocytic), PD31, 38B9 (murine preB), NFS 5.3 (murine late preB)	Elf-1	GCAGGAAGCA	m	(Akbarali *et al*., 1996; Grant *et al*., 1995)
Ig J-chain	HeLa	PU.1	AGCAGAAGCA	m	(Shin and Koshland, 1993)
Ig κ enhancer	S194 (Plasmacytoma)	PU.1	TGAGGAACTG	m	(Judde and Max, 1992; Pongubala *et al*., 1993)
Murine Ig λ2-4 Enhancer	J558L (myeloma)	PU.1	AAAGGAAGTG	m	(Eisenbeis *et al*., 1993)
Ig μ heavy chain	COS, NIH3T3	PU.1, ETS1	TGGGGAAGGG	m,f	(Erman and Sen, 1996; Nelsen *et al*., 1993; Rao *et al*., 1997; Rivera *et al*., 1993)
π, PreBCell specific IgH enhancer	HAFTL, PD31 (pre B)	EBS	GCAGGAAGCA	m	(Libermann and Baltimore, 1993)
V κ19	S194, Namalwa	PU.1	CTTCCTTATT	m	(Schwarzenbach *et al*., 1995)

Continued

Table 1 (*Continued*)

Promoter	*Tissue/Cell line*	*ETS gene*	*EBS*	*Assay*	*References*
Perforin (cytolytic T-cells)	CTLL-2, J588L (B lymph), P815 (mastocytoma), YAC-1 (TCL), EL-4 (thymoma)	EBS	CATGGAAACC	d,m,f	(Koizumi *et al*., 1993; Youn *et al*., 1996; Zhang and Lichtenheld, 1997)
Lysozyme	HD11 (transformed chicken myelomonocytes)	PU.1, Mef	TGAGGAACTA	d,m,	(Ahne and Stratling, 1994; Kai *et al*., 1999)
SCL (stem cell leukemia gene) Tal-1	MST (mast cells) F4N MEL	PU.1, Elf-1	TCCTTCCCCT CTTTTCCCCT	d,m	(Bockamp *et al*., 1995, 1998)
EOS47 (eosinophil marker)	Q2BN (fibroblasts)	ETS1	AATTTCCTAG	d,m	(McNagny *et al*., 1998)
Macrosialin (macrophage-specific)	RAW, THP-1, U937	PU.1	AAGGGAAGTG	d,m	(Li *et al*., 1998)
Transferrin	MEL	EBS	TCAGGAAGTG	m	(Lok and Ponka, 2000)
Cytosolic glutatione peroxidase	MEL	EBS	MS	d,m	(O'Prey *et al*., 1993)
Gp91^{phox} (Glycoprotein component of NADPH oxidase)	Jurkat, HEL	PU.1	CATTTCCTCA	m	(Suzuki *et al*., 1998; Voo and Skalnik, 1999)
p47^{phox} NADPH oxidase component	THP-1 HeLa, PLB 985	PU.1, Elf-1	GACTTCCTCT	d,m	(Li *et al*., 1999b)
HNP-defensin-1 (neutrophil specific antibiotic)	HL-60	PU.1	CCCGGAAATT	d,m	(Ma *et al*., 1998)
		Epithelial			
EndoA (type II keratin)	NIH3T3	Ets1, Ets2, Fli1	MS	g,t	(Seth *et al*., 1994)
Cytokeratin EndoA	PYS-2 (endodermal)	Ets2	ACAGGAAGTA GTAGGAACAG	m	(Fujimura *et al*., 1994)
Keratin 18	F9 (embryonal carcinoma)	EBS	AGCGGATGTG	m	(Pankov *et al*., 1994a,b; Rhodes and Oshima, 1998)
Keratin 18 Enhancer	Liver	Ets2	AGCGGATGTG	meth	(Umezawa *et al*., 1997)
SPRR1A (keratinocyte differentiation)	Fibroblasts, NIH3T3	EBS	TGAGGAATGA TATTTCCTTG	d,m	(Sark *et al*., 1998)
SPRR2A envelope protein (keratinocyte)	C-33A (cervical carcinoma)	Ese-1 (Esx, Ert)	GCAGGAAGTG	m	(Oettgen *et al*., 1997)
Profilaggrin	NHEK, HeLa	EBS	TTAGGAATGA	d	(Jang *et al*., 2000)
WAP	HC11 (murine mammary epithelial)	EBS	GAAGGAAGTG	m	(McKnight *et al*., 1995; Welte *et al*., 1994)
		Angiogenesis/Endothelial			
Flt-1 (VEGF R1)	293E1, HeLa	Ets1, Ets2, Erg	GTAGGAAGTG	d,m	(Wakiya *et al*., 1996)
Flk-1 (VEGF R2)	BAEC	EBS	MS	d	(Kappel *et al*., 1999)
Tie1	LE-II (lung endothelial), BEND (brain endothelial)	Ets1, Ets2	MS	d,m	(Iljin *et al*., 1999)
Tie2	Primary bovine aortic EC (BAEC)	Nerf2	MS	d,m	(Dube *et al*., 1999; Hewett *et al*., 1998; Schlaeger *et al*., 1997)
Endothelial nitric oxide synthase	BAEC	Ets1	TTGTTCCTGT	d,m	(Karantzoulis-Fegaras *et al*., 1999)
Endoglin (CD 105)	BAEC, HUVEC	PU.1	CACTTCCTCG	d,m	(Rius *et al*., 1998)
Thrombomodulin	HUVEC	Ets1, Ets2	MS	d	(von der Ahe *et al*., 1993)
VE Cadherin	BAEC, NIH3T3	EBS	ACAGGAAACC AAGGGAAGTA	m	(Gory *et al*., 1998)
		Other			
Vimentin	MCF7, MDA 231	E1AF > Erg > Ets1	GCAGGAAGGC	m	(Chen *et al*., 1996)
Tenascin-C	Human Fibroblasts	Fli1	AGAGGAAGGA	d,m	(Shirasaki *et al*., 1999)
Terminal Transferase	Immature T, B cells	Elf-1, Ets1, Fli1	GCAGGAAGTTG	m	(Ernst *et al*., 1993, 1996)
Glutathione-S-transferase	HepG2	EBS	CTTGGAAATG	m	(Ainbinder *et al*., 1997)
DNA glycosylase (DNA ex. repair)	H4IIE (rat hepatoma)	EBS	TGGGGAAAGC	d	(Grombacher and Kaina, 1996)
NAchR β43 enhancer	PC12	Ets1, Ets2	CAAGGAAATG CAAGGAAGTG	d,m	(McDonough *et al*., 2000)
Neurophilament Light gene	P19	EBS	GCAGGAATTT	g	(Pospelov *et al*., 1994)
Apolipoprotein	HepG2	GABP	CCCGGAAGCT	m	(Cardot *et al*., 1994; Yang *et al*., 1998b)

Continued

Table 1 (*Continued*)

Promoter	*Tissue/Cell line*	*ETS gene*	*EBS*	*Assay*	*References*
Cytochrome c oxidase Subunit IV	Cos, NIH3T3	GABP	TTCTTCCGGT	d,m	(Carter and Avadhani, 1994; Carter *et al*., 1992; Virbasius and Scarpulla, 1991)
Tyrosine aminotransferase	Cos	Ets1	ACAGGATGTT ACAGGATGTT	d, ivf	(Espinas *et al*., 1994)
Surf-1/2 (housekeeping)	HeLa	EBS	CCCGGAAGTG	meth	(Gaston and Fried, 1995a,b)
Thymidylate Synthase	3T6 (mouse fibroblasts)	EBS	AACTTCCGGC	d,m	(Liao *et al*., 1994)
Folate-Binding Protein	NIH3T3	GABP	AGAGGAAGGA AAGGGAAGGA	m	(Sadasivan *et al*., 1994)
Mitochondrial ATP-synthase β-subunit	HepG2	Ets1, Ets2	MS	d,m	(Villena *et al*., 1994)
Lysophospholipase		EBS	TGAGGAAACC CCCTTCCTCC	d	(Gomolin *et al*., 1993)
Third promoter of 6-Phosphofructo-2-kinase	FTO2B (rat hepatoma)	EBS	CCCGGAAGTG	d,m	(Dupriez *et al*., 1993)
Phosphoglycerate kinase 2	Testes	EBS	AAAGGAAATC	d	(Goto *et al*., 1993)
Osteoponin (bone matrix)	NIH3T3	EBS	GGAGGAAGTG	d,m	(Sato *et al*., 1998)
Peripherin	PC12	EBS	GCAGGAGGAA GGTTTCCTTC	m	(Chang and Thompson, 1996)
β-Enolase (muscle specific)	C2C12 (murine myoblasts)	EBS	ACAGGAAACG	d,m	(Taylor *et al*., 1995)
16α-hydroxylase (male specific)	HepG2	GABP	CTATTCCGGG	d, meth	(Yokomori *et al*., 1995)
HRS (SR protein, splicing factor)	HepG2, NIH3T3	GABP	CCCGGAAGTG	d,m	(Du *et al*., 1998)
Cardiac α-Myosin Heavy Chain	Cardiac Myocytes	EBS-Repressor	CCTGGAAGTG GTCTTCCCTG	m	(Gupta *et al*., 1998)
Tom-1 (unknown function)	QT6 (quail fibroblasts)	Ets1, Ets2	CATATCCTCT	m	(Burk and Klempnauer, 1999)
Heme Oxygenase	*Xenopus* oocytes	Erg, Fli1, Ets1	MS	d	(Deramaudt *et al*., 1999)
Ribosomal Protein L_{32}		PU.1	GCCGGAAGTG	e	(Yoganathan *et al*., 1992)
L14, ribosomal protein	*Xenopus* oocytes	XrpF1 (GABP)	ACCGGAAGTT	m,e	(Marchioni *et al*., 1993)
Antisense FGF-2 transcript	Jurkat	EBS	AACTTCCGGG	d	(Gagnon *et al*., 1999)

d: deletions, m: mutation, e: EMSA; t: transfection of promoter-reporter, meth: methylation interference, f: footprinting, ivf: *in vivo* footprinting, MS: multiple (>2) EBS. This table provides a list of those target genes that have been confirmed by functional assays (i.e. transfection of reporter constructs linked to putative promoters with mutated or deleted EBS). In a few cases where functional assessments were not available, targets that were validated with *in vitro* assays (i.e. EMSA or footprinting) are also included

complementary RNA and DNA based approaches *in vitro* and *in vivo*.

RNA-based approaches

Efforts to identify Ets target genes have often been based upon analysis of expression following gain or loss of function. Gain of function experiments employ constitutive or inducible expression of a family member, followed by identification of differentially expressed genes. Tetracycline-inducible expression of p42-Ets1 leads to increased expression of Caspase 1, which may account in part for the Fas- and low serum-induced apoptosis in the Ets1 expressing cells (Li *et al*., 1999a). Several approaches are available to identify gene expression differences including subtraction hybridization, differential display, representational difference analysis (RDA) and more recently, serial analysis of gene expression (SAGE) and Expression Array Analysis. Candidate target genes identified by this approach can subsequently be evaluated in the knockout mutant mice (loss of function). Enforced expression experiments may result in aberrant expression level and distribution, leading to identification of invalid target genes. It is noteworthy that most of the presumptive Myc target genes identified by gain of function studies were found not to have altered expression in the Myc knockout (Bush *et al*., 1998). This apparent discrepancy may be a reflection of cell-type specificity, cell cycle dependence, growth conditions or other experimental conditions.

Use of knockout/transgenic mice as models for identification of Ets target genes

The candidate target gene approach is based upon the biology of an Ets gene. Such an approach may be coupled with phenotypes observed in knockout and transgenic mice. Loss of function PU.1 results in absence of monocyte/macrophage development and B cells with abnormal T-cell and granulocytic development. Consistent with the myeloid phenotype, Northern analyses demonstrated that homozygous ($^{-/-}$) mutant PU.1 mice have greatly reduced levels of mRNAs for the receptors for M-CSF, G-CSF and GM-CSF. Each of these receptors had been previously proposed to be PU.1 responsive. However, a RDA study allowed for the identification of additional myeloid genes ((Iwama *et al*., 1998) and references within). Similarly, the megakaryocytic lineage defects observed with the recent Fli1 knockout mice (Hart *et al*., 2000; Spyropoulos *et al*., 2000) suggests that genes whose expression is necessary for this lineage may be Fli1 targets. RT–PCR studies demonstrate that gpIX (Hart *et al*., 2000) and c-mpl (Kawada *et al*., manuscript submitted) are reduced in mRNAs prepared

from homozygous mutant mice, consistent with earlier *in vitro* studies (Alexander and Dunn, 1995; Bastian *et al*., 1999; Deveaux *et al*., 1996). Caution is warranted however, since loss of a particular lineage may affect the expression of indirect target genes as well. Furthermore, tissue-specific alterations in presumptive target genes can occur as demonstrated by the initial RNase protection analysis of Ets2($^{-/-}$) mice (Yamamoto *et al*., 1998).

The transgenic (gain of function) animals that have been generated for Fli1 (Zhang *et al*., 1995), Ets2 (Sumarsono *et al*., 1996), PU.1 (Moreau-Gachelin *et al*., 1996) and TEL-PDEFβ (Ritchie *et al*., 1999) will potentially facilitate target gene identification. However, the transgenic approach will not provide as unambiguous a result as creating mice lacking expression of a specific Ets factor. First, the transgenic will have normal expression of the endogenous Ets factor, in addition to transgene expression. Second, improper timing, tissue context and level of ectopic expression may seriously compromise the value of the results using a transgenic approach.

One caveat/limitation to RNA based studies is that both direct and indirect target genes are identified. Expression of direct target genes is due to the interaction of Ets proteins with the regulatory elements present in the gene. In contrast, the regulation of indirect target genes may be controlled via proteins encoded by direct target genes. While kinetic arguments (time course of induction of a presumptive direct target gene relative to the expression of the Ets factor) can be used, an alternative approach to demonstrate direct regulation of a gene is the utilization of ER fusion constructs (Littlewood *et al*., 1995). Fusion of the estrogen receptor hormone binding domain (ER-HBD) to other proteins has been shown to result in ligand-dependent inducible activity of the resultant chimeric protein. Thus, in the absence of the ligand, the chimeric protein is expressed, but sequestered in the cytoplasm. Functional activity of the protein is dependent upon hormone addition and subsequent nuclear localization. Simultaneous addition of cycloheximide and hormone allows activation of target genes in the absence of protein synthesis and thus provides a method to distinguish primary and secondary target genes. One limitation to this approach is that not every protein fused ER turns out to be regulatable by ligand. In addition, in some cases, fusion of the ER domain to the amino terminus of the protein works better than fusion at the carboxy terminus (Trevor Littlewood, personal communications). Furthermore, such fusion protein may lose some of its ability to interact with its protein partners, which may also compromise experimental results. Although successful estrogen-mediated expression of ERM has been demonstrated (Pelczar *et al*., 1997), this chimeric protein has not yet been used to identify or validate ERM target genes. Not all attempts to develop hormone-regulated functionality will be successful. For example, we recently found that the human Fli1-Estrogen receptor fusion construct, joining the ER ligand binding domain to either the carboxy or amino terminal end of Fli1, was not regulated by hormone. Whether this was due in part to the observed functional interference between Fli1 and steroid hormone receptors (Darby *et al*., 1997) remains to be determined.

DNA based approaches

EMSA and *in vitro* footprinting assays have been used to demonstrate the potential for sequence-specific interaction between the labeled DNA and an Ets protein. To demonstrate *in vivo* Ets-DNA interactions, an early approach was analysis by *in vivo* footprinting (IVF). Sites of sequence-specific DNA-protein interactions are identified by altered reactivity to chemical modification in intact cells. Few studies have used this approach to evaluate whether an EBS is bound *in vivo* (Table 1, designated IVF). For example, IVF demonstrated cell type specificity of the functional EBS within the Rat tyrosine aminotransferase promoter (Espinas *et al*., 1994). However, *in vivo* footprinting studies do not allow identification of the specific Ets factor responsible for regulation of a given target. Other methodologies, such as whole-genome PCR and chromatin immunoprecipitation, have begun to be used for identification of targets for specific Ets factors. These methods allow the cloning of genomic DNA, based upon the presence of binding sites for a particular transcription factor.

Whole genome polymerase chain reaction (WGPCR)

WGPCR is one method that identifies direct target gene promoters/enhancer sequences for DNA binding proteins (Watson *et al*., 2000). Briefly, genomic DNA fragments are immuno-selected based upon their binding to a specific transcription factor and amplified by the polymerase chain reaction. The utility of WGPCR for the identification of Ets1 factor binding sites has been demonstrated. Among the clones isolated, three genomic fragments were found to be derived from the regulatory regions of the human serglycin, preproapolipoprotein C II and the Egr1 genes. Furthermore, the promoters of each of these genes contain consensus EBS able to bind to Ets proteins in EMSAs (Robinson *et al*., 1997).

Chromatin immunoprecipitation (ChIPs)

Chromatin immunoprecipitation is an exciting approach for the identification of target genes based upon *in vivo* occupancy of a promoter by a transcription factor and enrichment of transcription factor bound chromatin by immunoprecipitation using antibody against a specific transcription factor (Orlando, 2000). With this approach, cells are incubated with formaldehyde to crosslink proteins to DNA, and sonicated chromatin is subsequently incubated with Ets specific antibody or 'no antibody' control. Washed immunoprecipitates are analysed by PCR to determine whether candidate target genes are enriched in the Ets-immunoprecipitated samples. This approach has recently been used to demonstrate that the Rb gene is bound by Fli1 *in vivo* (Tamir *et al*., 1999). Another recent study utilizing ChIPs has demonstrated that following LPS stimulation, multiple Ets factors (Elk1, Ets1/2) are bound to the TNFα promoter *in vivo* (Tsai *et al*., 2000). It is important that ChIPs data be coupled with independent verification of the functional im-

portance of the binding sites identified. Furthermore, DNA based approaches do not allow to immediately distinguish the direction of the interaction of a transcription factor (repression or activation) with the particular promoter.

Ets target genes: future directions

We will soon be able to generate libraries of Ets-specific target genes using *in vivo* chromatin immunoprecipitation. Subsequent DNA sequence analysis should begin to allow identification of specific combinations of EBS proximal to binding sites for other transcription factors, allowing for better definition of Ets target genes. Perhaps ChIP approaches using multiple antibodies, used sequentially, may allow identification of *in vivo* synergistic interactions previously implicated by transient transfection assays or never before identified. The role of post-translational modifications upon complex formation may be able to be evaluated *in vivo* using phosphorylation or acetylation specific antibodies, followed by Ets factor-specific antibodies.

Similarly, ChIPs provides a valuable approach to assess the *in vivo* kinetics of Ets factor binding to specific promoter sites and to assess whether single or multiple family members can bind a single promoter. It will be important to determine whether Ets factor occupancy on specific promoters is altered during differentiation of specific lineages in normal development. We know that temporal specific expression of Ets factors occurs during development. Whether such changes can be correlated with differences in occupancy of Ets target gene promoters and subsequent gene expression remains to be determined. For example, such studies may demonstrate whether TEL can compete directly with the transcriptional targets of Fli1, as well as indirectly block Fli1 transcriptional activity (Kwiatkowski *et al*., 1998). Perhaps similar interplay between other Ets factors may also serve as a molecular switch between gene repression and activation and *vice versa*. The stable integration of specific promoter constructs provides a possible experimental system to simultaneously examine transcriptional activity and transcription factor occupancy (Boyd and Farnham, 1999).

Co-localization studies

Confocal microscopy with double immunostaining is an approach to confirm the co-localization of an Ets factor with its presumptive target gene within a particular set of cells within a specific tissue. From such analyses, we will determine if there are Ets-dependent expression patterns for specific target genes that may be evident in a tissue or temporal specific manner. It is anticipated that in some tissues, expression of specific target genes would have an absolute requirement for a specific Ets factor and these genes would not be expressed in these tissues in the appropriate Ets homozygous knockout mice. On the other hand, in some tissues, the expression of Ets may not be absolutely required, suggesting that redundancy between Ets family transcription factors may be tissue-specific. Indeed, precise examination of the tissue and cellular expression of target genes in wild-type and homozygous mutant mice is likely to be the only way to identify tissue-specific redundant pathways. Initial analysis of target gene expression in the Ets2 knockout mouse clearly illustrates this complexity. Tissue-specific loss of expression was observed for several of the genes whose expression was altered; for example, Ets1, MMP3, MMP9 and uPA were found to be reduced in the skin, while the mRNAs for these genes were apparently unchanged in the mammary gland (Yamamoto *et al*., 1998). It remains to be determined whether different cell types (e.g., basal cells versus epithelia cells versus stromal cells) in a particular tissue have identical Ets factor and/or target gene profiles.

Trap approaches for the identification of target genes

Future studies may exploit an inducible gene trap approach similar to that recently used to identify homeoprotein-regulated loci (Mainguy *et al*., 2000) for identification of Ets-responsive genes. Briefly, independent clones are isolated from a library of ES cells constructed to have randomly integrated reporters under the control of the individual 'trapped' gene promoters (promoter trap). To identify an Ets responsive gene, single cell clones can be incubated with purified fusion protein, consisting of the Ets domain of a specific Ets factor fused to the third helix of the homeodomain for efficient internalization into the ES cell. The internalized recombinant protein should compete with endogenous Ets proteins binding to EBS present in Ets-responsive genes expressed in ES cells. This approach should enrich for fusion transcripts corresponding to the Ets responsive genes. In addition, since each clone in the library is in ES cells, this method could also allow for rapid generation of knockout mice for specific Ets-target genes.

Modifiers of Ets function

Genetic screens for modifiers of Ets function will further enhance our understanding of the mechanisms that control the expression of Ets target genes. Such studies could be initiated using one of the eight *Drosophila* Ets genes (see article in this issue, Hsu and Schulz). Both gain of function and loss of function phenotypes provide foundations for screening for modifiers of phenotype (Rebay *et al*., 2000). Availability of the complete sequence of the *Drosophila* genome and the use of *Drosophila* genetics (Rubin and Lewis, 2000) will provide an approach to identify modifiers of Ets function (as well as a means to identify targets). Once identified, these genes may serve as probes for the identification of relevant mammalian target genes and modulators of Ets transcription factors (Ashburner *et al*., 2000).

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References

Ahne B and Stratling WH. (1994). *J. Biol. Chem.,* **269,** 17794–17801.
Ainbinder E, Bergelson S, Pinkus R and Daniel V. (1997). *Eur. J. Biochem.,* **243,** 49–57.
Akbarali Y, Oettgen P, Boltax J and Libermann TA. (1996). *J. Biol. Chem.,* **271,** 26007–26012.
Albanese C, Johnson J, Watanabe G, Eklund N, Vu D, Arnold A and Pestell RG. (1995). *J. Biol. Chem.,* **270,** 23589–23597.
Alexander WS and Dunn AR. (1995). *Oncogene,* **10,** 795–803.
Amato SF, Nakajima K, Hirano T and Chiles TC. (1996). *J. Immunol.,* **157,** 146–155.
Ansieau S, Plaza S, Ferreira E, Dozier C and Stehelin D. (1993). *Genomics,* **18,** 537–545.
Ashburner M, Ball CA, Blake JA, Botstein D, Butler H, Cherry JM, Davis AP, Dolinski K, Dwight SS, Eppig JT, Harris MA, Hill DP, Issel-Tarver L, Kasarskis A, Lewis S, Matese JC, Richardson JE, Ringwald M, Rubin GM and Sherlock G. (2000). *Nat. Genet.,* **25,** 25–29.
Aurigemma RE, Blair DG and Ruscetti SK. (1992). *J. Virol.,* **66,** 3056–3061.
Avots A, Hoffmeyer A, Flory E, Cimanis A, Rapp UR and Serfling E. (1997). *Mol. Cell. Biol.,* **17,** 4381–4389.
Bamberger AM, Erdmann I, Bamberger CM, Jenatschke SS and Schulte HM. (1997). *Mol. Cell. Endocrinol.,* **127,** 71–79.
Bastian LS, Kwiatkowski BA, Breininger J, Danner S and Roth G. (1999). *Blood,* **93,** 2637–2644.
Bastian LS, Yagi M, Chan C and Roth GJ. (1996). *J. Biol. Chem.,* **271,** 18554–18560.
Beier F, Taylor AC and LuValle P. (1999). *J. Biol. Chem.,* **274,** 30273–30279.
Berland R and Wortis HH. (1998). *J. Immunol.,* **161,** 277–285.
Besser D, Presta M and Nagamine Y. (1995). *Cell Growth Differ.,* **6,** 1009–1017.
Block KL, Shou Y and Poncz M. (1996). *Blood,* **88,** 2071–2080.
Blumenthal SG, Aichele G, Wirth T, Czernilofsky AP, Nordheim A and Dittmer J. (1999). *J. Biol. Chem.,* **274,** 12910–12916.
Boccia LM, Lillicrap D, Newcombe K and Mueller CR. (1996). *Mol. Cell. Biol.,* **16,** 1929–1935.
Bockamp EO, Fordham JL, Gottgens B, Murrell AM, Sanchez MJ and Green AR. (1998). *J. Biol. Chem.,* **273,** 29032–29042.
Bockamp EO, McLaughlin F, Murrell AM, Gottgens B, Robb L, Begley CG and Green AR. (1995). *Blood,* **86,** 1502–1514.
Boehlk S, Fessele S, Mojaat A, Miyamoto NG, Werner T, Nelson EL, Schlondorff D and Nelson PJ. (2000). *Eur. J. Immunol.,* **30,** 1102–1112.
Bosselut R, Duvall JF, Gegonne A, Bailly M, Hemar A, Brady J and Ghysdael J. (1990). *EMBO J.,* **9,** 3137–3744.
Botelho FM, Edwards DR and Richards CD. (1998). *J. Biol. Chem.,* **273,** 5211–5218.
Bottinger EP, Shelley CS, Farokhzad OC and Arnaout MA. (1994). *Mol. Cell. Biol.,* **14,** 2604–2615.
Boyd KE and Farnham PJ. (1999). *Mol. Cell. Biol.,* **19,** 8393–8399.
Bradford AP, Conrad KE, Wasylyk C, Wasylyk B and Gutierrez-Hartmann A. (1995). *Mol. Cell. Biol.,* **15,** 2849–2857.
Bradford AP, Wasylyk C, Wasylyk B and Gutierrez-Hartmann A. (1997). *Mol. Cell. Biol.,* **17,** 1065–1074.
Buras JA, Reenstra WR and Fenton MJ. (1995). *Mol. Immunol.,* **32,** 541–554.
Burk O and Klempnauer KH. (1999). *Biochim. Biophys. Acta,* **1446,** 243–252.
Bush A, Mateyak M, Dugan K, Obaya A, Adachi S, Sedivy J and Cole M. (1998). *Genes Dev.,* **12,** 3797–3802.
Buttice G, Duterque-Coquillaud M, Basuyaux JP, Carrere S, Kurkinen M and Stehelin D. (1996). *Oncogene,* **13,** 2297–2306.
Buttice G and Kurkinen M. (1993). *J. Biol. Chem.,* **268,** 7196–7204.
Cardot P, Pastier D, Lacorte JM, Mangeney M, Zannis VI and Chambaz J. (1994). *Biochemistry,* **33,** 12139–12148.
Carter RS and Avadhani NG. (1994). *J. Biol. Chem.,* **269,** 4381–4387.
Carter RS, Bhat NK, Basu A and Avadhani NG. (1992). *J. Biol. Chem.,* **267,** 23418–23426.
Carvalho M and Derse D. (1993). *J. Virol.,* **67,** 3885–3890.
Castillo AI, Tolon RM and Aranda A. (1998). *Oncogene,* **16,** 1981–1991.
Cederberg A, Hulander M, Carlsson P and Enerback S. (1999). *J. Biol. Chem.,* **274,** 165–169.
Chan YJ, Chiou CJ, Huang Q and Hayward GS. (1996). *J. Virol.,* **70,** 8590–8605.
Chang L and Thompson MA. (1996). *J. Biol. Chem.,* **271,** 6467–6475.
Chapman SC, Ayala JE, Streeper RS, Culbert AA, Eaton EM, Svitek CA, Goldman JK, Tavar JM and O'Brien RM. (1999). *J. Biol. Chem.,* **274,** 18625–18634.
Chen HM, Pahl HL, Scheibe RJ, Zhang DE and Tenen DG. (1993). *J. Biol. Chem.,* **268,** 8230–8239.
Chen HM, Ray-Gallet D, Zhang P, Hetherington CJ, Gonzalez DA, Zhang D-E, Moreau-Gachelin F and Tenen DG. (1995). *Oncogene,* **11,** 1549–1560.
Chen JH, Vercamer C, Li Z, Paulin D, Vandenbunder B and Stehelin D. (1996). *Oncogene,* **13,** 1667–1675.
Chiang SY, Burli RW, Benz CC, Gawron L, Scott GK, Dervan PB and Beerman TA. (2000). *J. Biol. Chem.,* **275,** 24246–24254.
Choi SG, Yi Y, Kim YS, Kato M, Chang J, Chung HW, Hahm KB, Yang HK, Rhee HH, Bang YJ and Kim SJ. (1998). *J. Biol. Chem.,* **273,** 110–117.
Chotani MA, Touhalisky K and Chiu IM. (2000). *J. Biol. Chem.,* **275,** 30432–30438.
Clark NM, Smith MJ, Hilfinger JM and Markovitz DM. (1993). *J. Virol.,* **67,** 5522–5528.
Coffer P, de Jonge M, Mettouchi A, Binetruy B, Ghysdael J and Kruijer W. (1994). *Oncogene,* **9,** 911–921.
Coles LS, Diamond P, Occhiodoro F, Vadas MA and Shannon MF. (2000). *J. Biol. Chem.,* **275,** 14482–14493.
Darby TG, Meissner JD, Ruhlmann A, Mueller WH and Scheibe RJ. (1997). *Oncogene,* **15,** 3067–3082.
Day RN, Liu J, Sundmark V, Kawecki M, Berry D and Elsholtz HP. (1998). *J. Biol. Chem.,* **273,** 31909–31915.
De Smet C, Courtois SJ, Faraoni I, Lurquin C, Szikora JP, De Backer O and Boon T. (1995). *Immunogenetics,* **42,** 282–290.
De Smet C, De Backer O, Faraoni I, Lurquin C, Brasseur F and Boon T. (1996). *Proc. Nat. Acad. Sci. USA,* **93,** 7149–7153.
Deramaudt BM, Remy P and Abraham NG. (1999). *J. Cell. Biochem.,* **72,** 311–321.
Deveaux S, Filipe A, Lemarchandel V, Ghysdael J, Romeo PH and Mignotte V. (1996). *Blood,* **87,** 4678–4685.
Dittmer J, Gegonne A, Gitlin SD, Ghysdael J and Brady JN. (1994). *J. Biol. Chem.,* **269,** 21428–21434.
Dittmer J, Gitlin SD, Reid RL and Brady JN. (1993). *J. Virol.,* **67,** 6087–6095.
Dittmer J and Nordheim A. (1998). *Biochim. Biophys. Acta,* **1377,** F1–11.
Dittmer J, Pise-Masison CA, Clemens KE, Choi KS and Brady JN. (1997). *J. Biol. Chem.,* **272,** 4953–4958.
Donahue JP, Sugg N and Hawiger J. (1994). *Biochim Biophys Acta,* **1219,** 228–232.

Donovan-Peluso M, George LD and Hassett AC. (1994). *J. Biol. Chem.,* **269,** 1361 – 1369.
Doubeikovski A, Uzan G, Doubeikovski Z, Prandini MH, Porteu F, Gisselbrecht S and Dusanter-Fourt I. (1997). *J. Biol. Chem.,* **272,** 24300 – 24307.
Du K, Leu JI, Peng Y and Taub R. (1998). *J. Biol. Chem.,* **273,** 35208 – 35215.
Dube A, Akbarali Y, Sato TN, Libermann TA and Oettgen P. (1999). *Circ. Res.,* **84,** 1177 – 1185.
Dupriez VJ, Darville MI, Antoine IV, Gegonne A, Ghysdael J and Rousseau GG. (1993). *Proc. Natl. Acad. Sci. USA,* **90,** 8224 – 8228.
Edelman GM, Meech R, Owens GC and Jones FS. (2000). *Proc. Natl. Acad. Sci. USA,* **97,** 3038 – 3043.
Egan BS, Lane KB and Shepherd VL. (1999). *J. Biol. Chem.,* **274,** 9098 – 9107.
Eichbaum QG, Iyer R, Raveh DP, Mathieu C and Ezekowitz RA. (1994). *J. Exp. Med.,* **179,** 1985 – 1996.
Eisenbeis CF, Singh H and Storb U. (1993). *Mol. Cell. Biol.,* **13,** 6452 – 6461.
Erman B and Sen R. (1996). *EMBO J.,* **15,** 4565 – 4575.
Ernst P, Hahm K and Smale ST. (1993). *Mol. Cell. Biol.,* **13,** 2982 – 2992.
Ernst P, Hahm K, Trinh L, Davis JN, Roussel MF, Turck CW and Smale ST. (1996). *Mol. Cell. Biol.,* **16,** 6121 – 6131.
Espinas ML, Roux J, Ghysdael J, Pictet R and Grange T. (1994). *Mol. Cell. Biol.,* **14,** 4116 – 4125.
Evans RM. (1988). *Science,* **240,** 889 – 895.
Ezashi T, Ealy AD, Ostrowski MC and Roberts RM. (1998). *Proc. Nat. Acad. Sci. USA,* **95,** 7882 – 7887.
Fears S, Gavin M, Zhang DE, Hetherington C, Ben-David Y, Rowley JD and Nucifora G. (1997). *Proc. Nat. Acad. Sci. USA,* **94,** 1949 – 1954.
Feinman R, Qiu WQ, Pearse RN, Nikolajczyk BS, Sen R, Sheffery M and Ravetch JV. (1994). *EMBO J.,* **13,** 3852 – 3860.
Fenrick R, Wang L, Nip J, Amann JM, Rooney RJ, Walker-Daniels J, Crawford HC, Hulboy DL, Kinch MS, Matrisian LM and Hiebert SW. (2000). *Mol. Cell. Biol.,* **20,** 5828 – 5839.
Flajolet M, Gegonne A, Ghysdael J, Tiollais P, Buendia MA and Fourel G. (1997). *Oncogene,* **15,** 1103 – 1110.
Foulds CE and Hawley DK. (1997). *Nucl Acids Res.,* **25,** 2485 – 2494.
Frampton J, Ramqvist T and Graf T. (1996). *Genes Dev.,* **10,** 2720 – 2731.
Fujimura Y, Yamamoto H, Hamazato F and Nozaki M. (1994). *Nucl. Acids Res.,* **22,** 613 – 618.
Fujitani Y, Nakajima K, Kojima H, Nakae K, Takeda T and Hirano T. (1994). *Biochem. Biophys. Res. Comm.,* **202,** 1181 – 1187.
Funaoka K, Shindoh M, Yoshida K, Hanzawa M, Hida K, Nishikata S, Totsuka Y and Fujinaga K. (1997). *Biochem. Biophys Res. Comm.,* **236,** 79 – 82.
Gagnon ML, Moy GK and Klagsbrun M. (1999). *J. Cell. Biochem.,* **72,** 492 – 506.
Gambarotta G, Boccaccio C, Giordano S, Ando M, Stella MC and Comoglio PM. (1996). *Oncogene,* **13,** 1911 – 1917.
Gaston K and Fried M. (1995a). *Gene,* **157,** 257 – 259.
Gaston K and Fried M. (1995b). *Nucl. Acids Res.,* **23,** 901 – 909.
Gegonne A, Bosselut R, Bailly RA and Ghysdael J. (1993). *EMBO J.,* **12,** 1169 – 1178.
Ghozi MC, Bernstein Y, Negreanu V, Levanon D and Groner Y. (1996). *Proc. Nat. Acad. Sci. USA,* **93,** 1935 – 1940.
Ghysdael J and Boureux A. (1997). *Oncogenes as Transcriptional Regulators, Vol. 1: Progress in Gene Expression.* Yaniv M and Ghysdael J (eds). Birkhauser Verlag: Basel, pp 29 – 88.
Gitlin SD, Bosselut R, Gegonne A, Ghysdael J and Brady JN. (1991). *J. Virol.,* **65,** 5513 – 5523.
Gomolin HI, Yamaguchi Y, Paulpillai AV, Dvorak LA, Ackerman SJ and Tenen DG. (1993). *Blood,* **82,** 1868 – 1874.
Gory S, Dalmon J, Prandini MH, Kortulewski T, de Launoit Y and Huber P. (1998). *J. Biol. Chem.,* **273,** 6750 – 6755.
Goto M, Masamune Y and Nakanishi Y. (1993). *Nucl. Acids Res.,* **21,** 209 – 114.
Gramolini AO, Angus LM, Schaeffer L, Burton EA, Tinsley JM, Davies KE, Changeux JP and Jasmin BJ. (1999). *Proc. Nat. Acad. Sci. USA,* **96,** 3223 – 3227.
Granger SW and Fan H. (1998). *J. Virol.,* **72,** 8961 – 8970.
Grant PA, Thompson CB and Pettersson S. (1995). *EMBO J.,* **14,** 4501 – 4513.
Graves BJ and Petersen JM. (1998). *Adv. Cancer Res.,* **75,** 1 – 55.
Gri G, Savio D, Trinchieri G and Ma X. (1998). *J. Biol. Chem.,* **273,** 6431 – 6438.
Grombacher T and Kaina B. (1996). *DNA and Cell Biology,* **15,** 581 – 588.
Groupp ER and Donovan-Peluso M. (1996). *J. Biol. Chem.,* **271,** 12423 – 12430.
Grove M and Plumb M. (1993). *Mol. Cell. Biol.,* **13,** 5276 – 5289.
Gum R, Lengyel E, Juarez J, Chen JH, Sato H, Seiki M and Boyd D. (1996). *J. Biol. Chem.,* **271,** 10672 – 10680.
Gunther CV and Graves BJ. (1994). *Mol. Cell. Biol.,* **14,** 7569 – 7580.
Gupta M, Zak R, Libermann TA and Gupta MP. (1998). *Mol. Cell. Biol.,* **18,** 7243 – 7258.
Gutman A and Wasylyk B. (1990). *EMBO J.,* **9,** 2241 – 2246.
Halle JP, Haus-Seuffert P, Woltering C, Stelzer G and Meisterernst M. (1997). *Mol. Cell. Biol.,* **17,** 4220 – 4229.
Hambor JE, Mennone J, Coon ME, Hanke JH and Kavathas P. (1993). *Mol. Cell. Biol.,* **13,** 7056 – 7070.
Harris VK, Liaudet-Coopman ED, Boyle BJ, Wellstein A and Riegel AT. (1998). *J. Biol. Chem.,* **273,** 19130 – 19139.
Hart A, Melet F, Grossfeld P, Chien K, Jones C, Tunnacliffe A, Favier R and Bernstein A. (2000). *Immunity,* **13,** 167 – 177.
Hashimoto Y and Ware J. (1995). *J. Biol. Chem.,* **270,** 24532 – 24539.
Henkel G and Brown MA. (1994). *Proc. Natl. Acad. Sci. USA,* **91,** 7737 – 7741.
Hermand P, Le Pennec PY, Rouger P, Cartron JP and Bailly P. (1996). *Blood,* **87,** 2962 – 2967.
Hewett PW, Daft EL and Murray JC. (1998). *Biochem. Biophys. Res. Commu.,* **252,** 546 – 551.
Heydemann A, Juang G, Hennessy K, Parmacek MS and Simon MC. (1996). *Mol. Cell. Biol.,* **16,** 1676 – 1686.
Hickey MJ and Roth GJ. (1993). *J. Biol. Chem.,* **268,** 3438 – 3443.
Hickstein DD, Baker DM, Gollahon KA and Back AL. (1992). *Proc. Nat. Acad. Sci. USA,* **89,** 2105 – 2109.
Higashino F, Yoshida K, Noumi T, Seiki M and Fujinaga K. (1995). *Oncogene,* **10,** 1461 – 1463.
Hilfinger JM, Clark N, Smith M, Robinson K and Markovitz DM. (1993). *J. Virol.,* **67,** 4448 – 4453.
Himelstein BP, Lee EJ, Sato H, Seiki M and Muschel RJ. (1997). *Oncogene,* **14,** 1995 – 1998.
Ho IC, Bhat NK, Gottschalk LR, Lindsten T, Thompson CB, Papas TS and Leiden JM. (1990). *Science,* **250,** 814 – 818.
Hoffmeyer A, Avots A, Flory E, Weber CK, Serfling E and Rapp UR. (1998). *J. Biol. Chem.,* **273,** 10112 – 10119.
Hohaus S, Petrovick MS, Voso MT, Sun Z, Zhang D-E and Tenen DG. (1995). *Mol. Cell. Biol.,* **15,** 5830 – 5845.
Holzmeister J, Ludewig B, Pauli G and Simon D. (1993). *Biochem. Biophys. Res. Commun.,* **197,** 1229 – 1233.

Howard PW and Maurer RA. (1995). *J. Biol. Chem.,* **270,** 20930–20936.
Iljin K, Dube A, Kontusaari S, Korhonen J, Lahtinen I, Oettgen P and Alitalo K. (1999). *FASEB J.,* **13,** 377–386.
Inaba T, Gotoda T, Ishibashi S, Harada K, Ohsuga J-I, Ohaski K, Yazaki Y and Yamada N. (1996). *Mol. Cell. Biol.,* **16,** 2264–2273.
Iwama A, Zhang P, Darlington GJ, McKercher SR, Maki R and Tenen DG. (1998). *Nucl Acids Res.,* **26,** 3034–3043.
Iwamoto S, Suganuma H, Kamesaki T, Omi T, Okuda H and Kajii E. (2000). *J. Biol. Chem.,* **275,** 27324–27331.
Jabrane-Ferrat N and Peterlin BM. (1994). *Mol. Cell. Biol.,* **14,** 7314–7321.
Jacob KK, Ouyang L and Stanley FM. (1995). *J. Biol. Chem.,* **270,** 27773–27779.
Jang SI, Karaman-Jurukovska N, Morasso MI, Steinert PM and Markova NG. (2000). *J. Biol. Chem.,* **275,** 15295–15304.
Jayaraman G, Srinivas R, Duggan C, Ferreira E, Swaminathan S, Somasundaram K, Williams J, Hauser C, Kurkinen M, Dhar R, Weitzman S, Buttice G and Thimmapaya B. (1999). *J. Biol. Chem.,* **274,** 17342–17352.
Johannsen E, Koh E, Mosialos G, Tong X, Kieff E and Grossman SR. (1995). *J. Virol.,* **69,** 253–262.
John S, Reeves RB, Lin JX, Child R, Leiden JM, Thompson CB and Leonard WJ. (1995). *Mol. Cell. Biol.,* **15,** 1786–1796.
Judde JG and Max EE. (1992). *Mol. Cell. Biol.,* **12,** 5206–5216.
Kai H, Hisatsune A, Chihara T, Uto A, Kokusho A, Miyata T and Basbaum C. (1999). *J. Biol. Chem.,* **274,** 20098–20102.
Kambe M, Miyamoto Y and Hayashi M. (1998). *Biochim. Biophys. Acta,* **1395,** 209–219.
Kamura T, Handa H, Hamasaki N and Kitajima S. (1997). *J. Biol. Chem.,* **272,** 11361–11368.
Kang R, Saito H, Ihara Y, Miyoshi E, Koyama N, Sheng Y and Taniguchi N. (1996). *J. Biol. Chem.,* **271,** 26706–26712.
Kappel A, Ronicke V, Damert A, Flamme I, Risau W and Breier G. (1999). *Blood,* **93,** 4284–4292.
Karantzoulis-Fegaras F, Antoniou H, Lai SL, Kulkarni G, D'Abreo C, Wong GK, Miller TL, Chan Y, Atkins J, Wang Y and Marsden PA. (1999). *J. Biol. Chem.,* **274,** 3076–3093.
Kaya M, Yoshida K, Higashino F, Mitaka T, Ishii S and Fujinaga K. (1996). *Oncogene,* **12,** 221–227.
Khurana TS, Rosmarin AG, Shang J, Krag TO, Das S and Gammeltoft S. (1999). *Mol. Biol. Cell.,* **10,** 2075–2086.
Kienker LJ, Ghosh MR and Tucker PW. (1998). *J. Immunol.,* **161,** 791–804.
Kistler B, Pfisterer P and Wirth T. (1995). *Oncogene,* **11,** 1095–1106.
Ko JH, Miyoshi E, Noda K, Ekuni A, Kang R, Ikeda Y and Taniguchi N. (1999). *J. Biol. Chem.,* **274,** 22941–22948.
Koizumi H, Horta MF, Youn BS, Fu KC, Kwon BS, Young JD and Liu CC. (1993). *Mol. Cell. Biol.,* **13,** 6690–6701.
Kominato Y, Galson D, Waterman WR, Webb AC and Auron PE. (1995). *Mol. Cell. Biol.,* **15,** 59–68.
Kondoh N, Yamada T, Kihara-Negishi F, Yamamoto M and Oikawa T. (1998). *Br. J. Cancer,* **78,** 718–723.
Kramer B, Wiegmann K and Kronke M. (1995). *J. Biol. Chem.,* **270,** 6577–6583.
Krehan A, Ansuini H, Bocher O, Grein S, Wirkner U and Pyerin W. (2000). *J. Biol. Chem.,* **275,** 18327–18336.
Kuprash DV, Osipovich OA, Pokholok DK, Alimzhanov MB, Biragyn A, Turetskaya RL and Nedospasov SA. (1996). *J. Immunol.,* **156,** 2465–2472.
Kwiatkowski BA, Bastian LS, Bauer Jr TR, Tsai S, Zielinska-Kwiatkowska AG and Hickstein DD. (1998). *J. Biol. Chem.,* **273,** 17525–17530.
Lambert PF, Ludford-Menting MJ, Deacon NJ, Kola I and Doherty RR. (1997). *Mol. Biol. Cell,* **8,** 313–323.
Laux G, Adam B, Strobl LJ and Moreau-Gachelin F. (1994). *EMBO J.,* **13,** 5624–5632.
Leduc I and Cogne M. (1996). *Mol. Immunol.,* **33,** 1277–1286.
Leiden JM, Wang CY, Petryniak B, Markovitz DM, Nabel GJ and Thompson CB. (1992). *J. Virol.,* **66,** 5890–5897.
Lepage A, Uzan G, Touche N, Morales M, Cazenave JP, Lanza F and de La Salle C. (1999). *Blood,* **94,** 3366–3380.
Leung S, McCracken S, Ghysdael J and Miyamoto NG. (1993). *Oncogene,* **8,** 989–997.
Li AC, Guidez FR, Collier JG and Glass CK. (1998). *J. Biol. Chem.,* **273,** 5389–5499.
Li R, Pei H and Papas T. (1999a). *Proc. Nat. Acad. Sci. USA,* **96,** 3876–3881.
Li SL, Schlegel W, Valente AJ and Clark RA. (1999b). *J. Biol. Chem.,* **274,** 32453–32460.
Li XR, Chong AS, Wu J, Roebuck KA, Kumar A, Parrillo JE, Rapp UR, Kimberly RP, Williams JW and Xu X. (1999c). *J. Biol. Chem.,* **274,** 35203–35210.
Liao WC, Ash J and Johnson LF. (1994). *Nucl. Acids Res.,* **22,** 4044–4049.
Libermann TA and Baltimore D. (1993). *Mol. Cell. Biol.,* **13,** 5957–5969.
Lin CS, Chang CH and Huynh T. (1997). *DNA Cell Biol.,* **16,** 9–16.
Lin CS, Chen ZP, Park T, Ghosh K and Leavitt J. (1993a). *J. Biol. Chem.,* **268,** 2793–2801.
Lin JX, Bhat NK, John S, Queale WS and Leonard WJ. (1993b). *Mol. Cell. Biol.,* **13,** 6201–6210.
Littlewood TD, Hancock DC, Danielian PS, Parker MG and Evan GI. (1995). *Nucl. Acids Res.,* **23,** 1686–1690.
Liu D, Pavlopoulos E, Modi W, Moschonas N and Mavrothalassitis G. (1997). *Oncogene,* **14,** 1445–1451.
Liu SH and Ng SY. (1994). *Biochem. Biophys. Res. Commun.,* **201,** 1406–1413.
Logan SK, Garabedian MJ, Campbell CE and Werb Z. (1996). *J. Biol. Chem.,* **271,** 774–782.
Lok CN and Ponka P. (2000). *J. Biol. Chem.,* **275,** 24185–24190.
Ma X, Neurath M, Gri G and Trinchieri G. (1997). *J. Biol. Chem.,* **272,** 10389–10395.
Ma Y, Su Q and Tempst P. (1998). *J. Biol. Chem.,* **273,** 8727–8740.
Mainguy G, Luz Montesinos M, Lesaffre B, Zevnik B, Karasawa M, Kothary R, Wurst W, Prochiantz A and Volovitch M. (2000). *Nat. Biotechnol.,* **18,** 746–749.
Manzanares M, Cordes S, Kwan CT, Sham MH, Barsh GS and Krumlauf R. (1997). *Nature,* **387,** 191–195.
Marchioni M, Morabito S, Salvati AL, Beccari E and Carnevali F. (1993). *Mol. Cell. Biol.,* **13,** 6479–6489.
Markiewicz S, Bosselut R, Le Deist F, de Villartay JP, Hivroz C, Ghysdael J, Fischer A and de Saint Basile G. (1996). *J. Biol. Chem.,* **271,** 14849–14855.
Markovitz DM, Smith MJ, Hilfinger J, Hannibal MC, Petryniak B and Nabel GJ. (1992). *J. Virol.,* **66,** 5479–5484.
Maul RS, Zhang H, Reid JDT, Pedigo NG and Kaetzel DM. (1998). *J. Biol. Chem.,* **273,** 33239–33246.
Maury W. (1994). *J. Virol.,* **68,** 6270–6279.
Mayall TP, Sheridan PL, Montminy MR and Jones KA. (1997). *Genes Dev.,* **11,** 887–899.
McCracken S, Leung S, Bosselut R, Ghysdael J and Miyamoto NG. (1994). *Oncogene,* **9,** 3609–3615.
McDonough J, Francis N, Miller T and Deneris ES. (2000). *J. Biol. Chem.,* **275,** 28962–28970.
McKinlay LH, Tymms MJ, Thomas RS, Seth A, Hasthorpe S, Hertzog PJ and Kola I. (1998). *J. Immunol.,* **161,** 4098–4105.

McKnight RA, Spencer M, Dittmer J, Brady JN, Wall RJ and Hennighausen L. (1995). *Mol. Endocrinol.,* **9,** 717–724.
McNagny KM, Sieweke MH, Doderlein G, Graf T and Nerlov C. (1998). *EMBO J.,* **17,** 3669–3680.
Melotti P and Calabretta B. (1994). *J. Biol. Chem.,* **269,** 25303–25309.
Minami T, Tachibana K, Imanishi T and Doi T. (1998). *Eur. J. Biochem.,* **258,** 879–889.
Miyajima I, Levitt L, Hara T, Bedell MA, Copeland NG, Jenkins NA and Miyajima A. (1995). *Blood,* **85,** 1246–1253.
Moreau-Gachelin F, Wendling, F, Molina T, Denis N, Titeux M, Grimber G, Briand P, Vainchenker W and Tavitian A. (1996). *Mol. Cell. Biol.,* **16,** 2453–2463.
Moulton KS, Semple K, Wu H and Glass CK. (1994). *Mol. Cell. Biol.,* **14,** 4408–4418.
Müller S, Sideras P, Smith CE and Santhopoulos KG. (1996). *Oncogene,* **13,** 1955–1964.
Munaut C, Salonurmi T, Kontusaari S, Reponen P, Morita T, Foidart JM and Tryggvason K. (1999). *J. Biol. Chem.,* **274,** 5588–5596.
Murakami K, Nomiyama H, Miura R, Follens A, Fiten P, Van Coillie E, Van Damme J and Opdenakker G. (1997). *DNA Cell Biol.,* **16,** 173–183.
Nakada M, Yamashita J, Okada Y and Sato H. (1999). *J. Neuropathol. Exp. Neurol.,* **58,** 329–334.
Nakajima K, Kusafuka T, Takeda T, Fujitani Y, Nakae K and Hirano T. (1993). *Mol. Cell. Biol.,* **13,** 3027–3041.
Nelsen B, Tian G, Erman B, Gregoire J, Maki R, Graves B and Sen R. (1993). *Science,* **261,** 82–86.
Nerlov C, Rorth P, Blasi F and Johnsen M. (1991). *Oncogene,* **6,** 1583–1592.
Nguyen VT and Benveniste EN. (2000). *J. Biol. Chem.,* **275,** 23674–23684.
Nimer S, Zhang J, Avraham H and Miyazaki Y. (1996a). *Blood,* **88,** 66–74.
Nimer SD, Zhang W, Kwan K, Wang Y and Zhang J. (1996b). *Blood,* **87,** 3694–3703.
Nishiyama C, Yokota T, Okumura K and Ra C. (1999). *J. Immunol.,* **163,** 623–630.
Nothias JY, Weinmann R, Blangy D and Melin F. (1993). *J. Virol.,* **67,** 3036–3047.
Noti JD, Reinemann C and Petrus MN. (1996). *Mol. Immunol.,* **33,** 115–127.
Nozawa M, Yomogida K, Kanno N, Nonomura N, Miki T, Okuyama A, Nishimune Y and Nozaki M. (2000). *Cancer Res.,* **60,** 1348–1352.
Nuchprayoon I, Meyers S, Scott LM, Suzow J, Hiebert S and Friedman AD. (1994). *Mol. Cell. Biol.,* **14,** 5558–5568.
Nuchprayoon I, Shang J, Simkevich CP, Luo M, Rosmarin AG and Friedman AD. (1999). *J. Biol. Chem,* **274,** 1085–1091.
Nuchprayoon I, Simkevich CP, Luo M, Friedman AD and Rosmarin AG. (1997). *Blood,* **89,** 4546–4554.
Oelgeschläger M, Nuchprayoon I, Lüscher B and Friedman AD. (1996). *Mol. Cell. Biol.,* **16,** 4717–4725.
Oettgen P, Alani RM, Barcinski MA, Brown L, Akbarali Y, Boltax J, Kunsch C, Munger K and Libermann TA. (1997). *Mol. Cell. Biol.,* **17,** 4419–4433.
Ohbo K, Takasawa N, Ishii N, Tanaka N, Nakamura M and Sugamura K. (1995). *J. Biol. Chem.,* **270,** 7479–7486.
Olsen J, Kokholm K, Troelsen JT and Laustsen L. (1997). *Biochem. J.,* **322,** 899–908.
O'Prey J, Ramsay S, Chambers I and Harrison PR. (1993). *Mol. Cell. Biol.,* **13,** 6290–6303.
Orlando V. (2000). *Trends Biochem. Sci.,* **25,** 99–104.
Pahl HL, Scheibe RJ, Zhang DE, Chen HM, Galson DL, Maki RA and Tenen DG. (1993). *J. Biol. Chem.,* **268,** 5014–5020.
Panitz F, Krain B, Hollemann T, Nordheim A and Pieler T. (1998). *EMBO J.,* **17,** 4414–4425.
Pankov R, Neznanov N, Umezawa A and Oshima RG. (1994a). *Mol. Cell. Biol.,* **14,** 7744–7757.
Pankov R, Umezawa A, Maki R, Der CJ, Hauser CA and Oshima RG. (1994b). *Proc. Nat. Acad. Sci. USA,* **91,** 873–877.
Park JS, Qiao L, Gilfor D, Yang MY, Hylemon PB, Benz C, Darlington G, Firestone G, Fisher PB and Dent P. (2000). *Mol. Biol. Cell.,* **11,** 2915–2932.
Pastorcic M and Das HK. (1999). *J. Biol. Chem.,* **274,** 24297–24307.
Pelczar H, Albagli O, Chotteau-Lelievre A, Damour I and de Launoit Y. (1997). *Biochem. Biophys. Res. Commun.,* **239,** 252–256.
Perez C, Coeffier E, Moreau-Gachelin F, Wietzerbin J and Benech PD. (1994). *Mol. Cell. Biol.,* **14,** 5023–5031.
Pokholok DK, Maroulakou IG, Kuprash DV, Alimzhanov MB, Kozlov SV, Novobrantseva TI, Turetskaya RL, Green JE and Nedospasov SA. (1995). *Proc. Nat. Acad. Sci. USA,* **92,** 674–678.
Pongubala JM, Van Beveren C, Nagulapalli S, Klemsz MJ, McKercher SR, Maki RA and Atchison ML. (1993). *Science,* **259,** 1622–1625.
Pospelov VA, Pospelova TV and Julien JP. (1994). *Cell Growth Differ.,* **5,** 187–196.
Postigo AA, Sheppard AM, Mucenski ML and Dean DC. (1997). *EMBO J.,* **16,** 3924–3934.
Prandini MH, Martin F, Thevenon D and Uzan G. (1996). *Blood,* **88,** 2062–2070.
Punturieri A, Shirakata Y, Bovolenta C, Kikuchi G and Coligan JE. (1993). *J. Immunol.,* **150,** 139–150.
Quan T and Fisher GJ. (1999). *J. Biol. Chem.,* **274,** 28566–28574.
Rao E, Dang W, Tian G and Sen R. (1997). *J. Biol. Chem.,* **272,** 6722–6732.
Rao S, Garrett-Sinha LA, Yoon J and Simon MC. (1999). *J. Biol. Chem.,* **274,** 34245–34252.
Ratajczak MZ, Perrotti D, Melotti P, Powzaniuk M, Calabretta B, Onodera K, Kregenow DA, Machalinski B and Gewirtz AM. (1998). *Blood,* **91,** 1934–1946.
Ray-Gallet D, Mao C, Tavitian A and Moreau-Gachelin F. (1995). *Oncogene,* **11,** 303–313.
Rebay I, Chen F, Hsiao F, Kolodziej PA, Kuang BH, Laverty T, Suh C, Voas M, Williams A and Rubin GM. (2000). *Genetics,* **154,** 695–712.
Reddy MA, Yang BS, Yue X, Barnett CJ, Ross IL, Sweet MJ, Hume DA and Ostrowski MC. (1994). *J. Exp. Med.,* **180,** 2309–2319.
Rehli M, Lichanska A, Cassady AI, Ostrowski MC and Hume DA. (1999). *J. Immunol.,* **162,** 1559–1565.
Rellahan BL, Jensen JP, Howcroft TK, Singer DS, Bonvini E and Weissman AM. (1998). *J. Immunol.,* **160,** 2794–2801.
Rhodes K and Oshima RG. (1998). *J. Biol. Chem.,* **273,** 26534–26542.
Ried S, Jager C, Jeffers M, Vande Woude GF, Graeff H, Schmitt M and Lengyel E. (1999). *J. Biol. Chem.,* **274,** 16377–16386.
Ritchie KA, Aprikyan AA, Bowen-Pope DF, Norby-Slycord CJ, Conyers S, Bartelmez S, Sitnicka EH and Hickstein DD. (1999). *Leukemia,* **13,** 1790–1803.
Rius C, Smith JD, Almendro N, Langa C, Botella LM, Marchuk DA, Vary CP and Bernabeu C. (1998). *Blood,* **92,** 4677–4690.
Rivera RR, Stuiver MH, Steenbergen R and Murre C. (1993). *Mol. Cell. Biol.,* **13,** 7163–7169.
Robinson L, Panayiotakis A, Papas TS, Kola I and Seth A. (1997). *Proc. Nat. Acad. Sci. USA,* **94,** 7170–7175.
Rodrigo I, Cato AC and Cano A. (1999). *Exp. Cell Res.,* **248,** 358–371.
Roebuck KA, Rahman A, Lakshminarayanan V, Janakidevi K and Malik AB. (1995). *J. Biol. Chem.,* **270,** 18966–18974.

Rorth P, Nerlov C, Blasi F and Johnsen M. (1990). *Nucl. Acids Res.,* **18,** 5009–5017.
Rosen GD, Barks JL, Iademarco MF, Fisher RJ and Dean DC. (1994). *J. Biol. Chem.,* **269,** 15652–15660.
Rosmarin AG, Caprio D, Levy R and Simkevich C. (1995a). *Proc. Nat. Acad. Sci. USA,* **92,** 801–805.
Rosmarin AG, Caprio DG, Kirsch DG, Handa H and Simkevich CP. (1995b). *J. Biol. Chem.,* **270,** 23627–23633.
Rosmarin AG, Luo M, Caprio DG, Shang J and Simkevich CP. (1998). *J. Biol. Chem.,* **273,** 13097–13103.
Ross IL, Yue X, Ostrowski MC and Hume DA. (1998). *J. Biol. Chem.,* **273,** 6662–6669.
Rubin GM and Lewis EB. (2000). *Science,* **287,** 2216–2218.
Rushton JJ, Zorich GP, Stolc V and Neudorf SM. (1997). *Eur. J. Biochem.,* **245,** 768–773.
Sadasivan E, Cedeno MM and Rothenberg SP. (1994). *J. Biol. Chem.,* **269,** 4725–4735.
Salmon P, Giovane A, Wasylyk B and Klatzmann D. (1993). *Proc. Natl. Acad. Sci. USA,* **90,** 7739–7743.
Sapi E, Flick MB, Rodov S and Kacinski BM. (1998). *Cancer Res.,* **58,** 1027–1033.
Sapru MK, Florance SK, Kirk C and Goldman D. (1998). *Proc. Nat. Acad. Sci. USA,* **95,** 1289–1294.
Sark MW, Fischer DF, de Meijer E, van de Putte P and Backendorf C. (1998). *J. Biol. Chem.,* **273,** 24683–24692.
Sato M, Morii E, Komori T, Kawahata H, Sugimoto M, Terai K, Shimizu H, Yasui T, Ogihara H, Yasui N, Ochi T, Kitamura Y, Ito Y and Nomura S. (1998). *Oncogene,* **17,** 1517–1525.
Savoysky E, Mizuno T, Sowa Y, Watanabe H, Sawada J, Nomura H, Ohsugi Y, Handa H and Sakai T. (1994). *Oncogene,* **9,** 1839–1846.
Sawada J, Simizu N, Suzuki F, Sawa C, Goto M, Hasegawa M, Imai T, Watanabe H and Handa H. (1999). *J. Biol. Chem.,* **274,** 35475–35482.
Schaeffer L, Duclert N, Huchet-Dymanus M and Changeux JP. (1998). *EMBO J.,* **17,** 3078–3090.
Schlaeger TM, Bartunkova S, Lawitts JA, Teichmann G, Risau W, Deutsch U and Sato TN. (1997). *Proc. Nat. Acad. Sci. USA,* **94,** 3058–3063.
Schwachtgen JL, Janel N, Barek L, Duterque-Coquillaud M, Ghysdael J, Meyer D and Kerbiriou-Nabias D. (1997). *Oncogene,* **15,** 3091–3102.
Schwarzenbach H, Newell JW and Matthias P. (1995). *J. Biol. Chem.,* **270,** 898–907.
Scott GK, Daniel JC, Xiong X, Maki RA, Kabat D and Benz CC. (1994). *J. Biol. Chem.,* **269,** 19848–19858.
Sementchenko VI, Schweinfest CW, Papas TS and Watson DK. (1998). *Oncogene,* **17,** 2883–2888.
Serdobova I, Pla M, Reichenbach P, Sperisen P, Ghysdael J, Wilson A, Freeman J and Nabholz M. (1997). *J. Exp. Med.,* **185,** 1211–1221.
Seth A, Robinson L, Panayiotakis A, Thompson DM, Hodge DR, Zhang XK, Watson DK, Ozato K and Papas TS. (1994). *Oncogene,* **9,** 469–477.
Seth A, Robinson L, Thompson DM, Watson DK and Papas TS. (1993). *Oncogene,* **8,** 1783–1790.
Sevilla L, Aperlo C, Dulic V, Chambard JC, Boutonnet C, Pasquier O, Pognonec P and Boulukos KE. (1999). *Mol. Cell. Biol.,* **19,** 2624–2634.
Shapiro LH. (1995). *J. Biol. Chem.,* **270,** 8763–8771.
Shelley CS, Farokhzad OC and Arnaout MA. (1993). *Proc. Natl. Acad. Sci. USA,* **90,** 5364–5368.
Shin MK and Koshland ME. (1993). *Genes Dev.,* **7,** 2006–2015.
Shirasaki F, Makhulf HA, LeRoy C, Watson DK and Trojanowska M. (1999). *Oncogene,* **18,** 7755–7764.
Sideras P, Muller S, Shiels H, Jin H, Khan WN, Nilsson L, Parkinson E, Thomas JD, Branden L, Larsson I and *et al.* (1994). *J. Immunol.,* **153,** 5607–5617.
Sieweke MH, Tekotte H, Jarosch U and Graf T. (1998). *EMBO J.,* **17,** 1728–1739.
Smith Jr MF, Carl VS, Lodie T and Fenton MJ. (1998). *J. Biol. Chem.,* **273,** 24272–24279.
Soldatenkov VA, Albor A, Patel BK, Dreszer R, Dritschilo A and Notario V. (1999). *Oncogene,* **18,** 3954–3962.
Spyropoulos DD, Pharr PN, Lavenburg KR, Jackers P, Papas TS, Ogawa M and Watson DK. (2000). *Mol. Cell. Biol.,* **20,** 5643–5652.
Stacey KJ, Fowles LF, Colman MS, Ostrowski MC and Hume DA. (1995). *Mol. Cell. Biol.,* **15,** 3430–3441.
Starck J, Doubeikovski A, Sarrazin S, Gonnet C, Rao G, Skoultchi A, Godet J, Dusanter-Fourt I and Morle F. (1999). *Mol. Cell. Biol.,* **19,** 121–135.
Steer JH, Kroeger KM, Abraham LJ and Joyce DA. (2000). *J. Biol. Chem.,* **275,** 18432–18440.
Stutz AM and Woisetschlager M. (1999). *J. Immunol.,* **163,** 4383–4391.
Sullivan J, Feeley B, Guerra J and Boxer LM. (1997). *J. Biol. Chem.,* **272,** 1943–1949.
Sumarsono SH, Wilson TJ, Tymms MJ, Venter DJ, Corrick CM, Kola R, Lahoud MH, Papas TS, Seth A and Kola I. (1996). *Nature,* **379,** 534–537.
Suzuki S, Kumatori A, Haagen IA, Fujii Y, Sadat MA, Jun HL, Tsuji Y, Roos D and Nakamura M. (1998). *Proc. Natl. Acad. Sci. USA,* **95,** 6085–6090.
Tajima A, Miyamoto Y, Kadowaki H and Hayashi M. (2000). *Biochim. Biophys. Acta,* **1492,** 377–384.
Takaoka AS, Yamada T, Gotoh M, Kanai Y, Imai K and Hirohashi S. (1998). *J. Biol. Chem.,* **273,** 33848–33855.
Tamir A, Howard J, Higgins RR, Li YJ, Berger L, Zacksenhaus E, Reis M and Ben-David Y. (1999). *Mol. Cell. Biol.,* **19,** 4452–4464.
Tanimura A, Teshima H, Fujisawa J and Yoshida M. (1993). *J. Virol.,* **67,** 5375–5382.
Taylor JM, Davies JD and Peterson CA. (1995). *J. Biol. Chem.,* **270,** 2535–2540.
Thomas RS, Tymms MJ, McKinlay LH, Shannon MF, Seth A and Kola I. (1997). *Oncogene,* **14,** 2845–2855.
Thomas RS, Tymms MJ, Seth A, Shannon MF and Kola I. (1995). *Oncogene,* **11,** 2135–2143.
Thompson AA, Wood Jr WJ, Gilly MJ, Damore MA, Omori SA and Wall R. (1996). *Blood,* **87,** 666–673.
Thompson CB, Wang CY, Ho IC, Bohjanen PR, Petryniak B, June CH, Miesfeldt S, Zhang L, Nabel GJ, Karpinski B and *et al.* (1992). *Mol. Cell. Biol.,* **12,** 1043–1053.
Tokino T, Thiagalingam S, el-Deiry WS, Waldman T, Kinzler KW and Vogelstein B. (1994). *Hum. Mol. Genet.,* **3,** 1537–1542.
Tommasi S and Pfeifer GP. (1995). *Mol. Cell. Biol.,* **15,** 6901–6913.
Townsend KJ, Zhou P, Qian L, Bieszczad CK, Lowrey CH, Yen A and Craig RW. (1999). *J. Biol. Chem.,* **274,** 1801–1813.
Tsai EY, Falvo JV, Tsytsykova AV, Barczak AK, Reimold AM, Glimcher LH, Fenton MJ, Gordon DC, Dunn IF and Goldfeld AE. (2000). *Mol. Cell. Biol.,* **20,** 6084–6094.
Turque N, Buttice G, Beuscart A, Stehelin D, Crepieux P and Desbiens X. (1997). *Int. J. Dev. Biol.,* **41,** 103–109.
Umezawa A, Yamamoto H, Rhodes K, Klemsz MJ, Maki RA and Oshima RG. (1997). *Mol. Cell. Biol.,* **17,** 4885–4894.
van Dijk TB, Baltus B, Caldenhoven E, Handa H, Raaijmakers JA, Lammers JW, Koenderman L and de Groot RP. (1998). *Blood,* **92,** 3636–3646.
Van Lint C, Ghysdael J, Paras Jr P, Burny A and Verdin E. (1994). *J. Virol.,* **68,** 2632–2648.
Venanzoni MC, Robinson LR, Hodge DR, Kola I and Seth A. (1996). *Oncogene,* **12,** 1199–1204.
Villena JA, Martin I, Vinas O, Cormand B, Iglesias R, Mampel T, Giralt M and Villarroya F. (1994). *J. Biol. Chem.,* **269,** 32649–32654.
Virbasius JV and Scarpulla RC. (1991). *Mol. Cell. Biol.,* **11,** 5631–5638.

von der Ahe D, Nischan C, Kunz C, Otte J, Knies U, Oderwald H and Wasylyk B. (1993). *Nucl Acids Res.,* **21,** 5636–5643.
Voo KS and Skalnik DG. (1999). *Blood,* **93,** 3512–3520.
Wakiya K, Begue A, Stehelin D and Shibuya M. (1996). *J. Biol. Chem.,* **271,** 30823–30828.
Wang CY, Bassuk AG, Boise LH, Thompson CB, Bravo R and Leiden JM. (1994a). *Mol. Cell. Biol.,* **14,** 1153–1159.
Wang LG, Liu XM, Li ZR, Denstman S and Bloch A. (1994b). *Cell Growth Differ.,* **5,** 1243–1251.
Wasylyk C, Gutman A, Nicholson R and Wasylyk B. (1991). *EMBO J.,* **10,** 1127–1134.
Watabe T, Yoshida K, Shindoh M, Kaya M, Fujikawa K, Sato H, Seiki M, Ishii S and Fujinaga K. (1998). *Int. J. Cancer,* **77,** 128–137.
Watson DK, Ascione R and Papas TS. (1990). *Crit. Rev. Oncog.,* **1,** 409–436.
Watson DK, Kitching R, Vary C, Kola I and Seth A. (2000). *Meth. Mol. Biol.,* **130,** 1–11.
Watson DK, Li R, Sementchenko VI, Mavrothalassitis G and Seth A. (2001). The ETS genes, Bertino, J. R. (Ed). *Encyclopedia of Cancer*. Academic Press.
Welte T, Garimorth K, Philipp S, Jennewein P, Huck C, Cato AC and Doppler W. (1994). *Eur. J. Biochem.,* **223,** 997–1006.
Wen SC, Ku DH, De Luca A, Claudio PP, Giordano A and Calabretta B. (1995). *Exp. Cell Res.,* **217,** 8–14.
Wilkinson NC and Navarro J. (1999). *J. Biol. Chem.,* **274,** 438–443.
Wotton D, Prosser HM and Owen MJ. (1993). *Leukemia,* **7,** S55–S60.
Yamamoto H, Flannery ML, Kupriyanov S, Pearce J, McKercher SR, Henkel GW, Maki RA, Werb Z and Oshima RG. (1998). *Genes Dev.,* **12,** 1315–1326.
Yan S, Berquin IM, Troen BR and Sloane BF. (2000). *DNA Cell Biol.,* **19,** 79–91.
Yan SF, Lu J, Zou YS, Soh-Won J, Cohen DM, Buttrick PM, Cooper DR, Steinberg SF, Mackman N, Pinsky DJ and Stern DM. (1999). *J. Biol. Chem.,* **274,** 15030–15040.
Yang C, Shapiro LH, Rivera M, Kumar A and Brindle PK. (1998a). *Mol. Cell. Biol.,* **18,** 2218–2229.
Yang Z, Boffelli D, Boonmark N, Schwartz K and Lawn R. (1998b). *J. Biol. Chem.,* **273,** 891–897.
Yang Z, Wara-Aswapati N, Chen C, Tsukada J and Auron PE. (2000). *J. Biol. Chem.,* **275,** 21272–21277.
Ying H, Chang JF and Parnes JR. (1998). *J. Immunol.,* **160,** 2287–2296.
Yoganathan T, Cowie A, Hassell JA and Sells BH. (1992). *Eur. J. Biochem.,* **207,** 195–200.
Yokomori N, Kobayashi R, Moore R, Sueyoshi T and Negishi M. (1995). *Mol. Cell. Biol.,* **15,** 5355–5362.
Youn BS, Kim KK and Kwon BS. (1996). *J. Immunol.,* **157,** 3499–3509.
Zhang C, Gadue P, Scott E, Atchison M and Poncz M. (1997a). *J. Biol. Chem.,* **272,** 26236–26246.
Zhang DE, Hetherington CJ, Chen HM and Tenen DG. (1994). *Mol. Cell. Biol.,* **14,** 373–381.
Zhang DE, Hohaus S, Voso MT, Chen HM, Smith LT, Hetherington CJ and Tenen DG. (1996). *Curr. Topics Microbiol. Immunol.,* **211,** 137–147.
Zhang L, Eddy A, Teng Y-T, Fritzler M, Kluppel M, Melet F and Bernstein A. (1995). *Mol. Cell. Biol.,* **15,** 6961–6970.
Zhang M, Maass N, Magit D and Sager R. (1997b). *Cell Growth Differ.,* **8,** 179–186.
Zhang M, Magit D and Sager R. (1997c). *Proc. Nat. Acad. Sci. USA,* **94,** 5673–5678.
Zhang Y and Lichtenheld MG. (1997). *J. Immunol.,* **158,** 1734–1741.