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Target gene context influences the transcriptional requirement for the KAT3 family of CBP and p300 histone acetyltransferases

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Abstract

One general principle of gene regulation is that DNA-binding transcription factors modulate transcription by recruiting cofactors that modify histones and chromatin structure. A second implicit principle is that a particular cofactor is necessary at all the target genes where the cofactor is recruited. Increasingly, these principles do not appear to be absolute, as experimentally defined relationships between transcription, cofactors, and chromatin modification grow in complexity. The KAT3 histone acetyltransferases CREB binding protein (CBP) and p300 have at least 400 interacting protein partners, thereby acting as hubs in gene regulatory networks. Studies using mutant primary cells indicate that the occurrence of CBP and p300 at any given target gene sometimes correlates with, rather than dictates transcription. This suggests that there are unexpected levels of redundancy between CBP/p300 and other unrelated coactivators, or that CBP/p300 recruitment may sometimes be coincidental. A transcription factor may therefore recruit the same group of coactivators as part of its "toolbox", but it is the characteristics of the individual target gene that determine which coactivation "tools" are required for its transcription.

Keywords

CBP; p300; histones; chromatin; transcription; coactivators; HAT

Traditional models of transcriptional activator and coactivator function

The transcriptional activation and repression of thousands of genes dictates and defines the differentiated state of the hundreds of cell types in mammals. Along with about 2,000 DNA-binding transcription factors, there are estimated to be more than 100 transcriptional coactivators and corepressors that regulate the expression of about 20,000 protein coding genes in the human genome.[1] At present, it is not entirely clear why there is so much potential for combinatorial complexity in mammalian transcriptional regulation. Probably a large variety of available coactivators provides redundancy, combinatorial regulatory potential, and tissue- and signal-specific regulation.[2–4]

Specific DNA sequences and the transcription factors that bind to them are the major regulators of gene expression. Bound at the gene promoter or enhancer, the activation (or repression) domains of the transcription factor recruit transcriptional cofactors such as coactivators or corepressors by protein-protein interactions. It is generally thought that the correctly positioned enzymatic and protein-binding activities of these coactivators stimulate transcription.[5] Patterns of gene expression then arise largely from synergistic or antagonistic interactions that occur when various combinations of DNA-bound transcription factors and cofactors assemble at each

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gene. In this scenario, transcriptional coactivators are largely utilitarian, providing enzymatic or adaptor functions to the regulatory-specificity defined by DNA-bound transcription factors. Implicit in these traditional models of transcription factor function is the idea that coactivators contribute to the transcription of all the target genes to which they are recruited. Hence the recent interest in mapping the occurrence of transcription factors, cofactors, and histone modifications in the genome using methods such as chromatin immunoprecipitation coupled with deep DNA sequencing (ChIP-seq).[6–8]

Less-traditional models of coactivator function

In contrast to traditional models of transactivation above, increasing evidence supports a model where coactivators may be recruited to promoters but are unequally utilized for the expression of genes in mammals. Recently for example, Toll-like receptor-responsive promoters that are rich in CpG dinucleotides were found to assemble unstable nucleosomes, which reduces their dependence on SWI/SNF nucleosome remodeling complexes.[9] In the case of CBP and p300, some hypoxia-responsive genes recruit but do not appear to require these histone acetyltransferases (HATs) for expression, and some NF-κB targets recruit CBP/p300 when not transcribed.[3, 10, 11] A specific interaction surface on CBP/p300 for the cAMP-responsive factor CREB is also differentially required for individual cAMP-responsive genes.[12] That coactivators like CBP/p300 provide gene-specific functions suggests another reason for cofactor diversity in mammals. Moreover, such non-customary models for coactivation are unexpected given how cofactors like CBP and p300 are believed to function biochemically. In the next several sections we will review aspects of HATs and histone acetylation to help place them in the context of these unconventional models of coactivation function.

CBP and p300 constitute the KAT3 family of HATs

There are four main multi-gene families of mammalian HATs based on sequence similarity (Ensembl database): GCN5 and PCAF (*Gcn5l2* and *Pcaf* in mice), the MYST family (*Htatip*, *Myst1*, *Myst2*, *Myst3*, and *Myst4*), the nuclear (or steroid) receptor coactivator family (*Ncoa1*, *Ncoa2*, *Ncoa3*, and sometimes including *Clock*) and the CBP and p300 family (*Crebbp* and *Ep300*) (Fig. 1).[13] In 2007, HATs were reclassified as KATs (lysine or K-acetyltransferases) to reflect their varied protein substrates and grouped into families similar to that in Ensembl (Fig. 1).[13] While HAT family members tend to share a high degree of sequence similarity, HAT domain sequences (and that of most other domains) are very dissimilar between families.[14] Such divergence between HAT families suggests that they evolved for functions distinct from just the acetylation of histones.

CBP (*Crebbp*) and *p300* (*Ep300*) encode highly related protein acetyltransferases that possess several conserved protein-binding domains [i.e., RID, CH1 (TAZ1), KIX, Bromodomain, PHD, HAT, ZZ, CH3 (TAZ2), and IBiD (NCBD)] that bind a variety of transcriptional regulators and other proteins (Figure 2).[15, 16] Indeed, distinct activators require different regions of p300 *in vitro*.[17] Both CBP and p300 occur in mammals, whereas *Drosophila* and *C. elegans* have only CBP, and yeast has neither.

The CBP-p300 interactome includes 400 interacting protein partners

CBP and p300 have at least 400 described interacting protein partners, making them among the most heavily connected nodes in the known mammalian protein-protein interactome (Table 1, internet search “CBP-p300 interactome” for an updated list with references). Analysis of global transcription networks in model organisms indicates that proteins that act as nodes or “hubs” are more likely to be encoded by essential genes.[18] Indeed, consistent with a role as hubs, both CBP and p300 are required for normal development and have been implicated in human disease.

CBP and *p300* mutations in Rubinstein-Taybi Syndrome (RTS)

RTS is a congenital developmental disorder, characterized by mental retardation, broad toes and thumbs, short stature, and facial anomalies.[19] In 1995, Petrij *et al*. identified RTS patients with heterozygous mutations in *CBP*, indicating that RTS is caused by a partial deficiency of CBP protein (i.e. haploinsufficiency).[20] A screen of 92 RTS patients revealed that 36 had mutations in *CBP* (including five missense mutations in the conserved HAT region) and three had mutations in *p300*.[21] The insufficient or altered functions of mutant CBP (and p300) that lead to RTS are unclear, although loss of HAT activity may be important.[22]

Consistent with critical roles in human development, *CBP* or *p300* nullizygous mice die during embryogenesis (day E8–E11), as do compound heterozygotes.[23, 24] The latter observation indicates that the combined amount of the two proteins is limiting. $p300^{+/-}$ mice tend to be small and less thrifty but are otherwise grossly normal (unpublished data).[24] Conversely, $CBP^{+/-}$ mice exhibit traits in common with RTS, including growth retardation and craniofacial anomalies, showing that many CBP developmental functions are conserved in mice and man.[25–30] Collectively, these studies support CBP and p300 as having gene network hub functions and reveal that they can have distinct roles in development.

Cells that lack CBP and p300

A cell type that can be stably sustained in the absence of both CBP and p300 has not yet been reported. The prevailing assumption is that some CBP or p300 protein is required for cell viability or proliferation, as shown for mouse lymphocytes *in vivo*.[31, 32] Consistent with this view, RNA interference (RNAi) mediated knockdown of CBP and p300 in immortal HeLa cells results in cell death due to “mitotic catastrophe” and “chromosome shredding.”[33] Similarly, RNAi knockdown of dCBP in Drosophila kc cells also leads to cell death.[34] These RNAi studies indicate that this approach is not generally applicable for knocking down CBP/p300 in cell lines for transcription experiments. Two recent studies have transiently reduced CBP and p300 levels by RNAi knock-down to investigate histone acetylation.[35, 36] Interestingly, these two papers show that the acetylation of histone H3 lysines K18 and K56 is highly dependent on CBP/p300, although effects on transcription were not reported.

Conditional knockout of CBP and p300

Since homozygous null mutations of either coactivator cause early embryonic lethality, the role of CBP and p300 in adult cell lineages remains largely unknown. Studies using conditional knockout CBP^{flox} and $p300^{flox}$ alleles indicate that both proteins play essential but distinct roles in hematopoiesis. Both genes contribute to antigen receptor signaling-responsive gene expression in T and B cells.[31, 32, 37] CBP and p300 are highly essential collectively but not individually for peripheral B cell homeostasis.[31] However, deletion of p300 before the pro-B-cell stage, using a *Mx-Cre* transgene, remarkably reduced B-cell numbers. In contrast, loss of either CBP or p300 during early T cell development results in a decrease in CD4 CD8 double-positive thymocytes.[32] Moreover, CBP mutant mice exhibit an increase in CD8 single positive thymocytes not seen in p300 mutants.[32] In fact, CBP appears to be vital to demarcate conventional and innate CD8+ T-cell development.[37] Conditional deletion of *CBP* has also provided insight into how it may function as a tumor suppressor. The T cell lymphomagenesis that results from loss of CBP in the T-cells of $MMTV\text{-}Cre;CBP^{flox/flox}$ mice occurs in synergy with p27 Kip1 insufficiency.[38] In addition to immune cell function, CBP and/or p300 also play essential roles in renin cells and primordial germ cells.[39, 40]

Hypomorphic mutations in *CBP* and *p300* show that their genome-unique domains are necessary for many but not all target genes

As CBP and p300 are essential for early mouse development, knock-in mutations in mice have been useful to further define their functions. Mutations that cause the loss of CBP or p300 histone acetyltransferase activity are dominant lethals that are detrimental to mouse development and transcription.[41, 42] Mice have also been created with point mutations in the KIX domains of CBP and p300 that inhibit their ability to bind the hematopoietic determining factor c-Myb and the cyclic-AMP- and calcium-responsive factor CREB.[43] The KIX domain of p300 is especially important for hematopoiesis, preventing the overproduction of platelets and megakaryocytes.[43] An independent study revealed that the increased platelets and megakaryocytes exhibited by ENU-induced *Plt6* mutant mice can be attributed to a Tyr to Asn substitution within the p300 KIX domain.[44] Targeted point mutations in the CBP KIX domain[43] highlight its importance in learning and memory, which are CREB-mediated processes.[45–47] Investigation of cAMP-inducible genes in primary mouse embryonic fibroblasts (MEFs) entirely deficient for normal KIX domains, reveals an unexpected spectrum of transcriptional responses.[12] While some cAMP-inducible genes are highly sensitive to the KIX mutations, others show only partial loss of activity or are unaffected. However, ChIP assays showed that cAMP-inducible recruitment of CBP or p300 to CREB target promoters was only partially blocked by the KIX mutation.[12] Therefore, KIX domain-independent recruitment of CBP/p300 to CREB may provide sufficient coactivation function to genes that are less transcriptionally affected by the KIX mutation.

Mutation of Ser436 in the CBP CH1 domain has been shown to increase CREB activity and liver gluconeogenesis in mice, suggesting this residue may negatively control the interaction between CREB and CBP.[48, 49] Indeed, phosphorylation of Ser436 is thought to be critical for lowering blood glucose in response to insulin or the anti-diabetic drug metformin by inhibiting the CREB-mediated transcription of gluconeogenic enzyme genes in the liver.[50] Interestingly however, MEFs homozygous for a deletion mutation in the CBP CH1 domain, but that retain Ser436 showed no obvious effect on CREB activity in transient assays.[11] In contrast, MEFs carrying the same knock-in deletions in both the CBP and p300 CH1 domain suggest that this region contributes to a sizable fraction of hypoxia-responsive gene expression.[11] Moreover, the CH1 domain is critical for the efficient recruitment of CBP/p300 to HIF-target genes in response to hypoxia. Together, studies of *CBP* and *p300* mutants have established their crucial roles in development and transcription, and have revealed that endogenous target genes do not have a uniform requirement for certain functions of the coactivators.

Mechanisms of transactivation by CBP and p300

It is thought that CBP and p300 can modulate transcription by five main mechanisms: acetylation of lysines in the N-terminal tails of histones, polyubiquitination[51] and acetylation of specific lysines on other transcriptional regulators, recruiting components of the Pol II machinery, and acting as adaptors to recruit other cofactors (e.g., coactivators). Currently, histone acetylation is considered to be the most important, or at least the most universal, of these mechanisms. However, which of these (or other) mechanisms are critical for the transactivation of endogenous target genes remains uncertain.

Histone acetylation correlates strongly with active transcription

More than 100 different modifications have been detected for the histones H2A, H2B, H3, and H4 that form the octamer of the typical nucleosome.[52] These include the eight main types of histone post-translational modifications, which are thought to alter chromatin structure or affect the recruitment of non-histone proteins: acetylation, methylation, phosphorylation,

ubiquitinylation, SUMOylation, ADP ribosylation, deimination, and proline isomerization.[53] The many different histone acetylation marks positively correlate with transcription[52] and in human T cells, the global recruitment of CBP, p300, and other HATs correlates strongly with both histone acetylation and the level of gene expression.[8]

One popular model of transcription states that a series of histone modifications occurs during transcription initiation and elongation, and that each modification is necessary for full gene expression.[54] Of all known modifications, acetylation would seem the most likely to "loosen" chromatin and facilitate transcription because it neutralizes the positive charge of lysines, thereby reducing the binding of histones to negatively charged DNA.[53] In this charge-neutralization model, the total amount of histone acetylation rather than the modification of particular residues would be critical. More recently a cofactor recruitment model was described where the acetylation of lysines 5, 8, and 12 of histone H4 recruits bromodomain containing protein-4 (Brd4), which is thought to be important for the induced expression of primary signal-responsive genes.[55]

Histone modifications in mammals – essential for transcription or just correlative?

There is broad consensus that certain histone modifications correlate strongly with gene activity but recent models incorporate increasing complexity to explain how histone marks regulate transcription.[54, 56] The multitude of histone modifications observed may indicate that they have one or more of these characteristics: 1) gene or context-restricted functions; 2) functional redundancy; or 3) status as non-functional "bystander" marks caused by enzymes that modify nonhistone proteins or are performing other functions.[52] Multiple alleles of each histone gene in mammals makes testing these models *in vivo* by mutagenesis extremely difficult, if not currently impossible.

Effects of histone mutations on gene expression in yeast

The extent to which any of the characteristics proposed above applies to histone acetylation in mammals is unclear. However, clues to the importance of histone modification for gene expression can be found from studies in baker's yeast. The viability of yeast strains with certain histone N-terminal tail deletion mutations, argues against a universal requirement for histone acetylation in gene regulation.[57–64] Moreover, expression defects are typically more gene-specific than genome-wide in these yeast mutants. Mutation of individual residues in histones H2A, H2B, H3, and H4 can also result in surprisingly moderate or specific defects in transcription.[61, 62, 65, 66] As for histone lysine acetylation, the individual mutation of K5, K8, or K12 of histone H4 in yeast has minor effects on transcription, whereas K16 has more unique functions.[65, 67] Combining these H4 mutations leads to cumulative changes in the expression of a group of genes, suggesting that acetylation can also act by affecting overall histone charge. Extrapolating these findings to mammals suggests that histone acetylation and (by inference) HATs are also not universally required for transcription.

Histone acetylating enzymes and activated transcription

What about the roles of histone-acetylating enzymes if it is uncertain why histone acetylation correlates strongly with active transcription? There are 13 known HAT genes in yeast, but only *ELP3* and *TAF1* are essential for cell viability, indicating that most, or perhaps all, HATs have redundant or specialized transcriptional functions (source: *Saccharomyces* Genome Database). It is unknown whether this is also true for mice. To date, mutant phenotypes for only 12 of the 20 known HAT genes have been reported (source: Jackson Laboratories, Mouse Genome Informatics (MGI)). Since mammalian HATs are often individually essential for embryo

development (which may be for a specific requirement in an essential cell type or for widespread requirements in many cells and processes), investigating the transcriptional roles of entire HAT families using conventional gene knockouts has been problematic or impossible. Certainly, the MGI database only reports phenotypes for mice with mutations in HAT genes that belong to the four major families defined in Figure 1. Moreover, the single instance in which both members of a HAT family were knocked out (GCN5 and PCAF) resulted in early embryonic lethality, preventing transcriptional analysis (Fig. 1).[68] Individually, *CBP* and *p300* knockouts (and compound heterozygotes) lead to embryonic lethality by E10.5 and anecdotal reports indicate the double-null phenotype is more severe, also preventing transcriptional analysis of this entire family.[24]

Conclusions

Histone N-terminal tail acetylation is a class of chromatin modification that strongly correlates with active transcription. Yet, the crucial functions that are fulfilled by HATs to stimulate transcription remain uncertain in mammals. There are at least 20 known HATs in mice and 13 of these belong to four multi-gene families. These HAT families share surprisingly little sequence identity within the acetyltransferase domain, and they have major differences in other functional domains. This diversity amongst HATs suggests that the bulk acetylation of histones is not their key function in gene activation. Moreover the recruitment of HATs such as CBP and p300 at a gene may not equate with a functional requirement for transcription. This suggests there is an unexpected level of redundancy between seemingly dissimilar transactivating cofactors and mechanisms.

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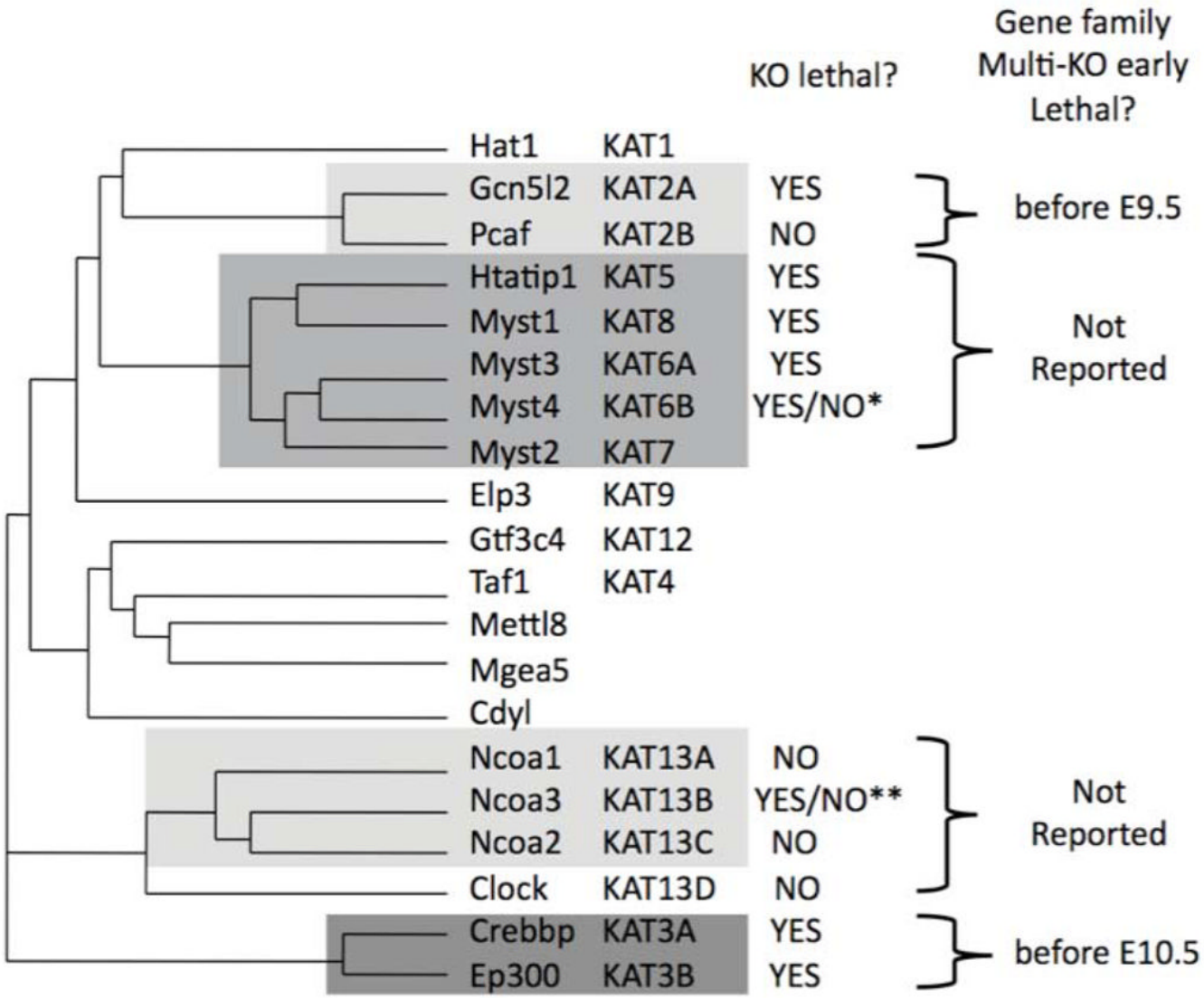

Figure 1.
Phylogram of 20 mammalian HAT proteins by clustalW sequence alignment and their KAT nomenclature. Shaded boxes indicate the gene families as defined by Ensembl. Reported lethality phenotypes are indicated for individual gene knockout mouse models and where possible for multi-gene family knockouts. * 2/3 of mice die by 1 month of age. **Increased mortality throughout lifespan.

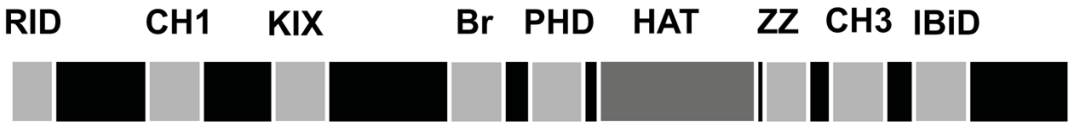

Figure 2.
CBP and p300 are closely related HATs that possess unique protein binding domains. Principal protein-binding domains of CBP and p300: nuclear receptor interaction domain (RID), the Cys/His-rich region 1 (CH1), the CREB-binding domain (KIX), bromodomain (Br), plant homeodomain (PHD), histone acetyltransferase domain (HAT), zinc-binding domain near the dystrophin WW domain (ZZ), the Cys/His-rich region 3 (CH3), and the interferon response factor-binding domain (IBiD).

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Table 1

The CBP and p300 interactome. 400 mammalian and viral proteins reported to interact physically or functionally with the KAT3 family members of CBP and p300. An updated and referenced list can be downloaded at www.stjude.org/brindle.

53BP1	CtBP1	H4	MN1	PGC-1a	SREBP1a
A-Myb	Ctbp2	HBZ	MR	PHOX2B	SREBP2
A238L	Cyclin D1	HCV core protein	Mre11	PIAS1	SRF
Actin	Cyclin E-Cdk2	HDAC1	MSG1	PIAS3	STAT1a
AhR	Dach1	HDAC6	Msh2	PIMT	STAT2
AIRE	Daxx	HEB	Msh6	Pit-1	STAT3
Akt	DBP	Hes6	Msx1	PLAG1	STAT4
AMF-1	DDX24	hHR23A	Msx3	PLAGL2	STAT5a
AML1	dHAND	Hic-5	MTF-1	PLZF	STAT5b
AP-2	E1A	HIF-1a	MyoD	PML	STAT6
Ap1b1	E2	HIPK2	mZac1b	Pol beta	Strap
APC5	E2F-1	HLF	N-Cadherin	POLR2A	Sug1
APC7	E2F-5	HNF-6	N-CoR	Polyoma large T	SV40 large T
APE1	E47	HNF1a	NAP-1	pp90 RSK	SYT
AR	E6	HNF1beta	NAP-2	PPARa	T-bet
Arnt	EBF	HNF4a	NBS1	PPARg	TAF1
ATF-1	EBNA2	HOXA10	NEDD1	PR	TAFII68
ATF-2	EBNA3C	HOXA11	NEMO	PRIC320	TAL1
ATF-4	Egr-1	HOXA9	Neuro D	PRMT5	Tat
ATG7	EID-1	HOXB1	NF-E2	ProTa	Tax
ATR	EID-2	HOXB2	NF-kB p50	Prox-1	TAZ
atrophin-1	EID3	HOXB3	NF-kB p65	PRS1	TBP
b-catenin	Eif2b1	HOXB4	NF-YA	PTEN	TCF-4N
B-Myb	EKLF	HOXB6	NFAT1	Ptf1a	TCL1
B56gamma3	Elk-1	HOXB7	NFATc1	PU.1	TDG
BAF47	Emb	HOXB9	NFATc4	pVHL	TFIIB
Bat3	ER81	HOXD10	NFI	Rad50	TFIIEb
BCL6	ERa	HOXD12	NFY-B	RAR	TFIIF
beta-TrCp1/Fbw1a	ERK2	HOXD13	Ngn1	Rb	TFIIIC

bICP0	ESE-1	HOXD4	Nished	RbAp48	TIF2	
BRCA1	Ets-1	HPV E7	Notch-1	RBCK1	TIP-1	
BRG1	Ets-2	HSF1	Nrf2	Rch1	TIP-2	
Bridge-1	EVI1	htt	NS1	RECQL4	TIP-3	
BRLF1	EWS	IKK-alpha	Nup93	RIP140	TIP-4	
Brn-2	Eya1	importin-a7	Nup98	RNA helicase A	TIP-5	
c-Fos	Eya3	ING2	Nur77	ROCK2	TIP-6	
c-Jun	Fbx3	IRF-1	OGG1	RORalpha	TIP-7	
c-Maf	Fen1	IRF-2	OLIG2	RSK2	TIP-8	
c-Myb	FGFR1	IRF-3	P-Lim	Runx2	TLS	
c-Myc	FHL2	IRF-7	P/CAF	Runx3	TLX1	
C/EBPa	FKLF2	JDP2	p/CIP	RXR	TP2	
C/EBPb	FOG-2	JMY	p100	Sam68	TR beta	
C/EBPd	FoxA2	JunB	p220(NPAT)	Sap-1a	TRBP	
C53	Foxl1	K8/K-bZIP	p28ING5	SATB1	TReP-132	
CARM1	FoxM1B	KLF2	p29ING4	SF-1	Trip10	
Cart1	FOXO1a	KLF4	p30(II)	SGK1	TSG101	
CAS	FOXO3a	KLF5	p33ING1b	Sh3gl1	TTF-1	
CD44	FOXO4	KLF6	p34SEI-1	SIRT1	Twist	
Cdc25B	FXR	Ku70	p35srj	SIRT2	UBF	
CDK8	GABPa	MafG	p38 MAPK	SKIP	VDR	
CDP	Gak	MAM	p53	Skn-1a	vIRF-1	
cdx-2	GAPDH	MAML2	P532	Skp2	VP16	
CFIm25	GATA-1	mArnt3	p63	Smad1	Vpr	
CHC	GATA-2	MASH1	p68 RNA helicase	Smad2	VRK1	
CIITA	GATA-3	MDC1	p73	Smad3	VRK2	
CITED4	GATA-4	MDM2	p8	Smad4	WRN	
CK2	GATA-5	MED25	PAP	Smad7	WT1	
Cnot3	GATA-6	MEF-2D	PARP-1	SMIF	XAF1	
CoAA	GCMa	MEF2C	pax-6	SNIP1	YAP	
CoCoA	GCN5	MEKK1	Pax3	Sox-2	YB-1	
COUP-TF II	Gli3	mGPBP	Pax5	SOX4	YY1	
CPAP	GMEB-1	Mi	Pax8	Sox9	ZBP-89	

CREB	GMEB-2	Mi-2beta	PC4	Sp1	ZBTB2
CREM	GR	MIER1	PCNA	Sp3	ZEB-1
CREST	H2A	Miz-1	PDX-1	Spi-B	ZNF639
CRTC2	H2B	MKP-1	PEA3	SRC1	
CRX	H3	MLL	PELP1	SRCAP	