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An analysis of genes regulated by the multi-functional transcriptional regulator Yin Yang-1

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INTRODUCTION

Yin Yang-1 (YY1) is a zinc finger protein (1) which posesses the unusual property of regulating transcription in three ways. In different gene contexts, YY1 has been shown to activate transcription, repress transcription or initiate transcription. The rapidly growing number of both cellular and viral genes which have YY1 binding sites in their transcriptional regulatory regions emphasizes the importance of YY1 as a transcriptional regulator. In addition, YY1 has recently been shown to associate with the c-Myc protein and this association inhibits the transcriptional activation and repression activities of YY1 (2). Thus the intriguing possibility exists that one function of the c-Myc oncoprotein may be to modulate the expression of YY1-dependent genes by virtue of its association with YY1.

In order to understand the scope of YY1 activity and to discern clues as to its mechanism(s) of action, we have surveyed all the currently known genes which contain YY1 binding sites and analyzed their YY1 binding sites. We have also summarized the present understanding of how YY1 modulates transcription of these genes. This analysis shows that the sequence of YY1 binding sites varies between YY1-dependent genes which are activated or repressed by YY1.

Structure and expression pattern of YY1

YY1 (UCRBP, δ, or NF-E1) is a zinc finger protein which contains four C_2H_2 zinc fingers belonging to the GLI-Kruppel family (1,3–5). As illustrated in Figure 1, the zinc fingers, located in the C-terminal portion of the protein, mediate sequence specific DNA binding of YY1 (4). The N-terminus of the protein contains an acidic region followed by an unusual run of histidine residues. When the entire YY1 protein is fused to the GAL4 DNA binding domain, the fusion protein functions as a transcriptional repressor (1); however when the N-terminal 90 amino acids are fused to the Gal4 DNA binding domain the fusion protein activates transcription (6). The function, if any, of the histidines alone is not known. An internal region between the N-terminal acidic region and the C-terminal zinc fingers, amino acids 201–333, is common to the regions required for protein–protein association between YY1 and Sp1 (7,8), between YY1 and c-Myc (2) and between YY1 and E1A (Y.Shi, personal communication) (Fig. 1).

YY1 RNA (3,4) and protein (14) appear to be widely expressed but little is presently known about possible regulation of YY1 RNA or protein levels or about how YY1 activity may be regulated post-translationally. However, YY1 protein is prone to proteolytic degradation (15) and during differentiation of chick myoblasts YY1 levels drop, possibly due to degradation (6,9). The YY1 decrease during myogenesis correlates with changes in the expression of two YY1-dependent genes: α-actin is activated and c-*myc* is repressed when YY1 levels fall (6,9) consistent with the fact that YY1 represses α-actin transcription (9) and activates c-*myc* transcription (16).

Association of YY1 with other proteins

In view of its pleotropic activities, it is not surprising that association with other proteins appears to be important in determining the activity of YY1. YY1 was first cloned because it bound to an E1A sensitive site in the Adenoassociated virus (AAV) P5 promoter (1). Adenovirus E1A protein associates directly with YY1 (2) and E1A relieves YY1-dependent repression at the P5 promoter, transforming YY1 into a transcriptional activator (1). YY1 also associates with another transcription activator Sp1; YY1 and Sp1 together activate transcription in a synergistic manner (7,8). In addition, studies using the P5 promoter in an *in vitro* system show that YY1, TFIIB and Pol II are sufficient to initiate transcription (17). There is also evidence for a physical association between YY1 and TFIIB and between YY1 and TBP but the regions of YY1 required for these associations have not been reported (17, A.Berrier and K.Calame, unpublished). Finally, a two-hybrid screen revealed that c-Myc associates with YY1 (2). In cotransfections, over-expression of c-Myc inhibits both the transcriptional activation and repression abilities of YY1. Since the 201–343 amino acid region required for YY1 association with c-Myc is also required for association with Sp1 and E1A, c-Myc may inhibit YY1 activity by interfering with its ability to associate with other transcription proteins. c-Myc levels vary in response to many mitogens and growth signals and it may be that varying levels of c-Myc modulate YY1 activity *in vivo*.

YY1 as an activator of transcription

YY1 is known to activate transcription of six cellular genes, one viral promoter and two promoters from cellular repetitive sequences which probably originated from viruses (Table I). The most obvious features of the cellular genes are that five of the

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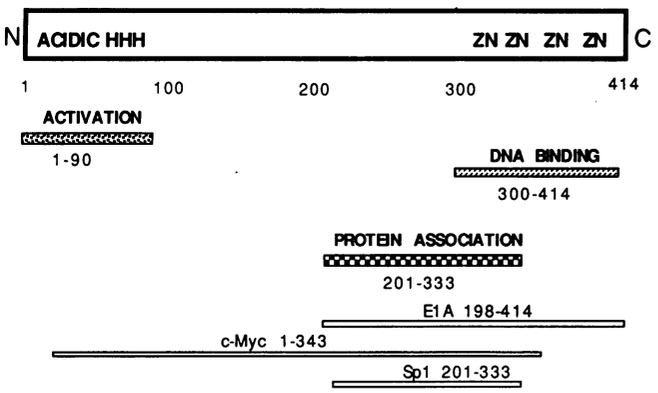


Figure 1. Functional domains of YY1. The approximate location of the acidic stretch, histines (HHH) and zinc fingers (Zn) are indicated within the rectangle representing YY1 protein. The numbers below the box indicate amino acids. The regions defined for transcriptional activation and DNA binding are indicated. The region common to association with three proteins is denoted 'protein association'; the region required for association with each individual protein is shown below.

six (excluding the immunoglobulin heavy chain gene) are expressed ubiquitously and three of the six are ribosomal protein genes. However, the small sample size makes it difficult to determine whether ubiquitous expression is a common feature of YY1-activated genes.

Little is known about the mechanism(s) by which YY1 activates transcription. The fact that YY1 binding sites for the three ribosomal protein genes (18–21), the IgH gene (14), the DHFR gene (28) and the LINE-1 transposon (25,26) all lie 3′ of the transcription initiation site suggests a common mechanism but there is no direct evidence for this possibility. Association between YY1 and TFIIB (17, A.Berrier and K.Calame, unpublished) or TBP (17) has been observed and may be important for the ability of YY1 to activate transcription. Sites with higher YY1 binding affinity have been shown to perform as better activator sites in cotransfections than sites with lower YY1 binding affinity (27).

YY1-dependent activation of c-*myc* transcription (16) is particularly interesting because c-Myc protein associates with YY1 and inhibits its transcriptional activation and repression activities (2). Inhibition of YY1's ability to activate c-*myc* transcription by the association of c-Myc protein with YY1 provides a molecular basis for the negative autoregulation of c-*myc* transcription which has been known for several years (29,30).

YY1 as a repressor of transcription

The seven cellular genes which are known to be repressed by YY1 are all highly regulated genes and six of them — Igκ, skeletal α-actin, ϵ-globin, MCK, serum amyloid and β-casein — are expressed in a tissue-specific manner (Table II). This pattern contrasts with the ubiquituously expressed cellular genes which are activated by YY1 but, as noted previously, the number of genes is still small and these emerging patterns are noted primarily to help guide future analyses as more YY1-dependent genes are identified and studied.

Table I. Genes where YY1 activates transcription

Cellular		
	IgH, intronic enhancer	(10,11)
	c-myc promoter	(14,16)
	rpL7 promoter	(4,21)
	rpL30 promoter	(4,18–21)
	rpL32 promoter	(4,18–21)
	DHFR promoter	(22)
Viral		
	HSV-1	(23,24)
	LINE-1 transposon	(25,26)
	IAP	(27)

Table II. Genes where YY1 represses transcription

Cellular		
	c-fos	(31,32)
	Ig kappa	(5,27)
	Skeletal α-actin	(9,33)
	ϵ-globin	(34,35)
	MCK (cardiac) (36)	
	β-casein	(37,38)
	Serum amyloid	(13)
Viral		
	HPV-18	(39)
	HPV-16	(40)
	AAV P5 promoter	(1)
	HIV LTR	(41)
	MoMuLV LTR	(3)
	CMV promoter/enhancer	(12)

YY1 also negatively regulates a growing number of viral genes; six are known at present (Table II). Its importance for Human Papillomavirus type 16 (HPV-16) is particularly striking. HPV-16 induces squamous intraepithelial lesions of the cervical mucosa which may develop into invasive cancer. The expression of viral oncogenes in advanced neoplasias increases relative to the proliferating cell layers of low grade lesions raising questions about molecular mechanisms responsible for deregulation of transcription. Recently, deletion or mutation of YY1 binding sites was found to be commonly used by HPV-16 to escape from the cellular repression in the cervical cancers thus suggesting an important role of YY1 in regulation of viral oncogenes (40). YY1-dependent repression in the long terminal repeats (LTRs) of two retroviruses, Moloney Murine Leukemia Virus (3) and Human Immunodeficiency Virus-1 (41), is intriguing but the mechanism by which repression occurs in these viruses is not well-understood at present.

Different mechanisms have been suggested for YY1's repressor activity. In the c-fos promoter there is evidence that repression is caused by the ~ 80° bend in the DNA which YY1 induces upon binding (32). It has been suggested that YY1-induced bending prevents interactions between upstream activators and the basal transcription machinery (BTM). When the orientation of one YY1 site is reversed, YY1 activates the c-fos promoter, probably by facilitating rather than preventing interaction between activators and the BTM.

However, the ability of YY1 to repress transcription seems unlikely to reside solely in its DNA binding and bending

Table III. Sequences of YY1 binding sites

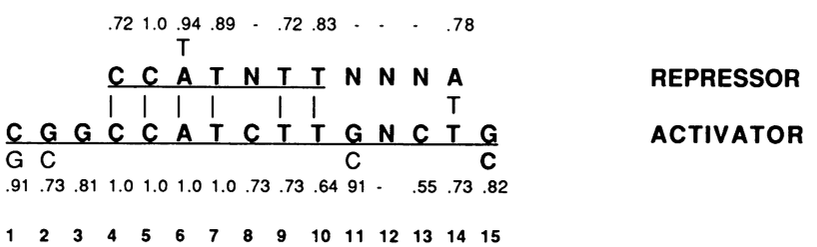
YY1 REPRESSOR SITES

G C G C C C C A T A C A A G G C G	MCK (-167 to -183) (36)
A G A A A C C A T T T T C T A A T	β Casein (-108 to -128) (37)
G A T G T C C A T A T T A G G A C	c-Fos 1 (-315 to -298) (32)
G G G G A C C A T C T C C G A A A	c-Fos 2 (-251 to -235) (32)
G A A G T C C A T C C A T T C A C	c-Fos 3 (-59 to -42) (32)
C G T C G C C A T A T T T G G G T	α Actin (-77 to -93) (9)
G G A T A T C A T T T T G G A A G	ε Globin (-274 to -258) (35)
C A C C T C C A T C T T G T T T G	Ig κ 3' Enh (5)
T C C C A C C A T G T C A T T T C	Serum amyloid (-105 to -88) (13)
A C T T T T C A T T A A T A C T T	HPV 18 (7847 to 7831) (39)
T G T C A C C C T A G T T C A T A	HPV 16-1 (7792 to 7776) (40)
A C A G T T C A T G T A T G A A C	HPV 16-2 (7802 to 7786) (40)
C A T G T G C A G T T T T A C A A	HPV 16-3 (7845 to 7829) (40)
C A C A C C C A T G T G C A G T T	HPV 16-4 (7851 to 7835) (40)
T T G C G A C A T T T T G C G A C	AAV P5 (-51 to -67)(1)
T A A C G C C A T T T T G C A A G	MoMuLV (7 to 23) (3)
T C T A A C C A G A G A G A C C C	HIV (+16 to -1) (41)
G A A T G C C A T T T A C C G G G	CMV (-512 to-495) (12)
N N N N N C C A T N T T N N N A N	**CONSENSUS**
A	
T	
- - - - - .72 1.0.94 .89 - .72 .83 - - - .78 -	

YY1 ACTIVATOR SITES

G A T C G G C C A T C T T G A C T C A A	IgH μ Enh (363-343) (14,50)
G C C C G A C C A T T T T C T C T T C T	c-Myc-1 (-247 to -267) (14)
A A T A C G C C A T G T A C C C T G G A	c-My-2 (-385 to -405) (14)
C C C C G G C C A T C T T G G C G G C T	rpL30 (11 to 31) (19)
T G G C T G C C A T C T G T T T T A C G	rpL32-1 (26 to 46) (19)
T G G C G G C C A T C C G C C G C C T G	rpL32-2 (58 to 78) (19)
C T G G A A C C A T G G A G G C T G T T	rpL7 (15 to 35) (21)
C C G C T G C C A T C A T G G T T C G A	DHFR (44 to 64) (28)
C C A G G G C C A T C T T G A A T G G A	HSV1VP5 (-60 to -80) (23)
A T T C G G C C A T C T T G G C T C C T	LINE-1 (26 TO 6) (25)
T C A G C G C C A T C T T G T A A G A T	IAP (-189 to -169) (27)
N N N C G G C C A T C T T G N C T G N N	**CONSENSUS**
G C C G	
- - - .91 .73 .81 1.0 1.0 1.0 1.0 .73 .73 .64 91 - .55 .73 .82 - -	

CONSENSUS SEQUENCES



Consensus sequences were derived by scoring any single base with a representation > 50% and any two bases = or > 75% at individual positions as a consensus. Fractional representation is indicated by the numbers below or above the corresponding position. When one of two bases is shown in bold, this indicates it is predominately present; if their frequency is similar, both are shown in bold.

properties since a GAL4−YY1 fusion protein, which binds to DNA via the GAL4 binding domain rather than the YY1 zinc fingers, also represses transcription in some cells (1,2). In addition, adenovirus E1A protein can reverse the repressor activity of YY1 at the AAV P5 promoter (1). While the mechanism by which E1A relieves repression is not clear, E1A does not bind DNA and it seems unlikely that E1A acts by altering the DNA bending induced by YY1 binding. In addition, repression by a GAL4 binding domain−YY1 fusion protein is also relieved by E1A, consistent with the idea that E1A alters repression by YY1 via a mechanism which does not involve binding of YY1 zinc fingers to DNA (1). Thus it seems likely that YY1 may repress transcription by more than one mechanism.

An emerging theme for genes where YY1 represses transcription is that YY1 sites often overlap or occur near an activator-binding site and that increased expression of the activator relieves YY1-dependent repression, possibly by displacing YY1. Six of the seven cellular genes repressed by YY1 (excluding Igκ), as well as the HPV-18 promoter, have YY1 sites which are near to or overlap with activator binding sites. The YY1 site in the c-fos promoter overlaps the binding site for serum response factor (SRF); YY1 and SRF compete for binding to the site (31). Similarly YY1 and SRF compete for binding in the α-actin promoter (9,31). Over-expression of SRF reverses YY1-mediated trans repression *in vivo* on both promoters (9,31). YY1 sites also overlap serum response elements in the M isozyme of the creatine kinase gene (36). In the β-casein gene the YY1 site overlaps with a site for Mammary Gland Factor (MGF), an activator which is induced by lactogenic hormones (37,38). The YY1 site in the liver acute phase response gene for serum amyloid overlaps with a NF-κB site (13). The gene is repressed by YY1 and YY1 is antagonized by NF-κB during the acute phase induction of NF-κB (13). Finally, the YY1 site in the ϵ-globin developmental stage-specific silencer abuts a GATA site and it has been suggested that the erythroid-specific activator GATA-1 may displace YY1 (35).

YY1 as an initiator of transcription

Two initiator elements have been shown to depend upon the binding activity of YY1 — the Adenoassociated Virus P5 promoter (AAV P5) (17,42) and the cytochrome oxidase Vβ subunit promoter (43). There have also been suggestions that YY1 sites may act as initiator or 'mitigator' sites in the HIV LTR, the AD12 major late promoter (44) and the DHFR promoter (45) but direct evidence for this is not currently available. However, it is intriguing to consider the possibility that YY1 binding sites in many contexts could be sites of transcription initiation.

At the AAV P5 promoter +1 site YY1 initiates transcription *in vitro* in a unique way which appears to be indepenent of TBP and depends only upon YY1, TFIIB and Pol II (17). Direct association between YY1 and TFIIB has been shown (17, A.Berrier and K.Calame, unpublished) and could be important for the ability of YY1 to initiate transcription and also to behave as a transcriptional activator. However the *in vivo* significance of YY1 initiating transcription in the absence of TBP is not clear because YY1 can physically associate with TBP and thus TBP is likely to play a role in YY1-mediated initiation *in vivo* (17).

The mechanism(s) by which initiator sites function is not well-understood. Recent mutagenesis studies on initiator sites suggest that YY1 and other initiator-binding proteins may act as accessories to another, currently uncharacterized, initiator-binding protein (46). It has also been shown that the ability of YY1 to initiate transcription is significantly enhanced when Sp1 sites are present upstream of the transcription initiation site and that YY1 and Sp1 physically associate and functionally synergize (7,8).

Analysis of YY1 binding sites

YY1 binding sites for elements where YY1 appears to activate transcription and for elements where YY1 appears to represses transcription have been compiled and separate consensus sequences have been derived (Table III). The experimental data and the degree of certainty regarding the function of individual YY1 sites used in this analysis vary. For example, in the rpL30 promoter where the YY1 ('delta') site was shown to be an activator site (19), later work suggested that mutation of the site caused no change in promoter activity (4). However, keeping this limitation in mind, several interesting features emerge from analysis of YY1 sites.

The previously published nine base consensus sequence for YY1 binding, G/CNCCATNTT (9), is, for the most part, confirmed by analysis of this larger sample. CCATNTT in the center of the sequence is the most highly conserved portion of the consensus for both activator and repressor site sequences. However, the activator consensus sequence is larger than the previously derived consensus and larger than the repressor site consensus as well. It contains 15 bp with only one internal site where the bases are not conserved. The core sequence, CCATCTT, is similar but not identical to that of the repressor sequence. Additional conserved bases flanking the activator core are predominantly G or C. By contrast, the consensus for the repressor sequence is only 7 bp. When the two consensus sequences are compared, it is clear that the activator consensus is not only longer but also more strongly conserved.

The activator consensus is also more GC-rich than the repressor consensus — compare bases 1, 2, 3, 8, 11, 13 and 15 in the activator consensus to comparable bases in the repressor sequence. Since zinc finger proteins in the C_2H_2 class have been shown to bind CG-rich sequences (47,48), this suggests that the activator sites may be tighter YY1-binding sites than the repressor sites. Although the relative affinities of all known YY1 sites have not been studied systematically, it has been shown that the activator IAP YY1 site has higher affinity for YY1 than the repressor sites in the 3′ kappa enhancer or the MoMuLV LTR (27), which is consistent with this suggestion. Furthermore, this idea is supported by the finding that substitution of A/T for G/C in position 3 or 11 decreases the binding affinity of YY1 for its site (46). Lower affinity binding could be intrinsically important to the mechanism by which YY1 represses transcription or could be necessary to allow YY1 at repressor sites to be displaced by activators. Alternatively, it may be that different DNA bases at YY1 binding sites are differentially bent, thus altering the overall effect of YY1 binding. These are interesting questions for future studies.

CONCLUSION

This analysis of YY1-dependent genes emphasizes the rapidly growing number of genes which have been found to be regulated by YY1. YY1 cDNA was first cloned in 1991 (1); since then YY1-binding sites have been identified in 28 genes. This number includes the genes discussed and analyzed above and also the 3′ immunoglobulin heavy chain enhancer (49), the α-globin promoter (52) and the Ad12 major late promoter (44) where the

function of YY1 sites is not established and the N-ras promoter (39) and the murine E2F1 promoter (51) where binding of YY1 is suggested by sequence homology but has not been demonstrated experimentally. It seems reasonable that the number of YY1-dependent genes will continue to grow. YY1-dependent cellular genes include important housekeeping genes, tissue-specific and highly regulated genes and proto-oncogenes. YY1 also regulates expression of retroviruses, herpes viruses and adeno-related viruses. Since elevated levels of the c-Myc oncoprotein modulate YY1 activity, some or all of the YY1-dependent genes may also be susceptible to regulation by c-Myc. In this review we have noted possible patterns in the kinds of genes which YY1 activates or represses and differences in the sequence of YY1 activator and repressor sites. These patterns should aid further identification and analysis of YY1-dependent genes.

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