Minireview

THE JOURNAL OF BIOLOGICAL CHEMISTRY
Vol. 274, No. 42, Issue of October 15, pp. 29583–29586, 1999
© 1999 by The American Society for Biochemistry and Molecular Biology, Inc.
Printed in U.S.A.

Context-dependent Transcriptional Regulation*

Christopher J. Fry and Peggy J. Farnham‡

From the McArdle Laboratory for Cancer Research, University of Wisconsin Medical School, Madison, Wisconsin 53706

Understanding the mechanisms by which the transcription rate of a particular gene is controlled is a common goal of many investigators. A general approach taken to study transcriptional regulation has been to first identify a protein-binding site(s) using methods such as DNase footprinting or gel mobility shift assays and then to remove the binding site(s) from its natural context by placing single or multiple copies of the site(s) upstream of a heterologous minimal promoter. This approach has the advantage that a large degree of transcriptional activity can be observed when multiple copies of a factor are brought to a promoter that can recruit very few other site-specific DNA-binding proteins. However, analysis of synthetic promoter constructs provides information concerning what a transcription factor has the potential to do but does not necessarily provide information about the specific contribution of a factor to the regulation of a natural promoter. Throughout the text, "context-dependent" transcriptional regulation refers to instances in which the transcriptional properties of a particular factor are influenced either by its position relative to other factors bound to a given promoter or by the abundance of transcriptional cofactors in a given cell type. It should be emphasized that context-dependent regulation can be lost when transferring a binding site to a heterologous promoter, when the position of a binding site is changed within a natural promoter, or when the cellular expression levels of critical transcriptional cofactors are altered. The purpose of this minireview is to describe various ways in which the specific context of a binding site in a promoter influences the ability of a DNA site-specific transcription factor to regulate gene expression. For simplicity, we have limited our examples to four different transcription factors: YY1, lymphocyte enhancer-binding factor 1 (LEF-1),[1] Sp1, and E2F.

YY1 is a ubiquitously expressed mammalian transcription factor that can function as an activator, a repressor, or an initiator protein, depending upon promoter context (1). YY1 binds to a specific DNA sequence element (CCATNTT) via a DNA-binding domain that contains four C-terminal zinc finger motifs of the Cys_2-His_2 class. YY1 can bend DNA, and it physically interacts with a variety of basal and site-specific transcription factors (p300, TATA-binding protein (TBP), TBP-associated factor (TAF) 55, TFIIB, RNA polymerase II, Sp1, c-Myc, and cAMP-regulated enhancer-binding protein (CREB) binding protein. These two characteristics are responsible for the fact that YY1 function, perhaps to a greater degree than many other transcription factors, is critically dependent upon promoter structure.

LEF-1 is a member of the T cell factor (TCF)/LEF family of transcription factors, which in mammals also includes TCF-1, TCF-3, and TCF-4 (2). Members of this family of transcription factors contain an 85-amino acid DNA-binding domain that is homologous to high mobility group (HMG) proteins. One subclass of HMG proteins has a high affinity for DNA structures containing sharply angled bends, four-way junctions, or crossovers; this subset of factors has little sequence specificity for DNA binding. LEF-1 is a member of a second subclass of HMG proteins, which binds to specific sequence elements that are variants of the consensus CCTTTGAA. The HMG factors are believed to modulate both gene expression and chromatin structure. The ability of LEF-1 to bend DNA contributes to its context-dependent activation properties.

Sp1 is a member of a family of transcription factors consisting of Sp1, Sp2, Sp3, and Sp4 (3). These proteins bind to GC-rich sequences (*e.g.* GGGCGG) found in the promoters of many cellular genes. Sp1 can activate transcription through a variety of mechanisms, functioning as both a basal promoter element and as an upstream activator, depending on promoter context. In many genes lacking TATA boxes, a proximally positioned Sp1 site serves as the critical determinant of promoter activity and positions the start site of transcription. However, Sp1 can also enhance transcription from a distance through DNA looping mediated by protein-protein interactions.

The E2F family of transcription factors functions as heterodimers that bind a consensus DNA sequence TTTSSCGC (S=C or G) (4). To date six different mammalian E2F proteins (E2F1–6) have been cloned, and each of these heterodimerizes with DP1 or DP2 proteins. The E2F proteins contain central DNA-binding and dimerization domains and (except for E2F6) a C-terminal transactivation domain. The DP proteins contribute to the DNA binding activity of the heterodimer but do not contain a transactivation domain. Nested within the transactivation domain of the E2F proteins is a protein interaction domain that mediates contact with the retinoblastoma (Rb) family of proteins (Rb, p107, and p130), which function to repress transcription. Thus, the interaction of E2F with Rb determines the activation and repression functions of an E2F heterodimer bound to a promoter and is critical for mediating cell cycle-regulated expression of E2F target genes.

Five Mechanisms by Which Context-dependent Transcriptional Activation Can Be Achieved

Transcription Factor-induced DNA Bending Can Influence Promoter Activity—Using simple synthetic promoters, Kim and Shapiro (5) have shown that a YY1 site can stimulate promoter activity if placed between a binding site for nuclear factor 1 (NF1) and a TATA box but not if the positions of the YY1 and NF1 sites are switched (Fig. 1*A*). These results suggest that the robust activity of the NF1-YY1-TATA promoter is not simply because of synergy of two weak transcriptional activation domains. Rather, the authors suggested that a YY1-induced DNA bend brings the NF1 protein in proximity to the basal transcription complex only if YY1 is placed between NF1 and the TATA box. To test this hypothesis, the rotational orientation of the YY1-induced bend was changed (by deleting 4 base pairs of DNA between YY1 and the TATA box) so that YY1 bent the NF1 site in the opposite direction. The synergy between YY1 and NF1 was lost, supporting the hypothesis that the YY1-induced bend is the critical determinant in activation of the promoter. However, a YY1-induced bend does not have the same function at all promoters. For example, a similar YY1-induced DNA bend represses transcription from the c-*fos* promoter (6) and can repress activating protein 1 (AP1)-mediated transcription from a synthetic AP1-YY1-TATA promoter (5). Thus, these studies show that, because of YY1-mediated DNA bending, changing the context of a YY1-binding site can dramatically change the effects of YY1 on promoter activity. The ability of LEF-1 to bend DNA can also

* This minireview will be reprinted in the 1999 Minireview Compendium, which will be available in December, 1999.

‡ To whom correspondence should be addressed: McArdle Laboratory, 1400 University Ave., Madison, WI 53706. Tel.: 608-262-2071; Fax: 608-262-2824; E-mail: farnham@oncology.wisc.edu.

[1] The abbreviations used are: LEF-1, lymphocyte enhancer-binding factor 1; TBP, TATA-binding protein; TAF, TBP-associated factor; CREB, cAMP-regulated enhancer-binding protein; TCF, T cell factor; HMG, high mobility group; Rb, retinoblastoma; NF1, nuclear factor 1; AP1, activating protein 1; TCRα, T-cell receptor α; SV40, simian virus 40; Egr, early growth response; PMA, phorbol 12-myristate 13-acetate; CDF-1, CDE-CHR binding factor-1; SRF, serum response factor; SRE, serum response element; NF-κB, nuclear factor of the κ light chain enhancer in B cells; OTF-1/Oct-1, octamer-binding transcription factor; GATA, GATA-binding factor; ALY, ally of LEF-1; TK, thymidine kinase; Inr, initiator; TdT, terminal deoxynucleotidyltransferase; VP16, herpes simplex virus virion protein 16; AAV P5, adeno-associated virus P5; APC, adenomatous polyposis coli.

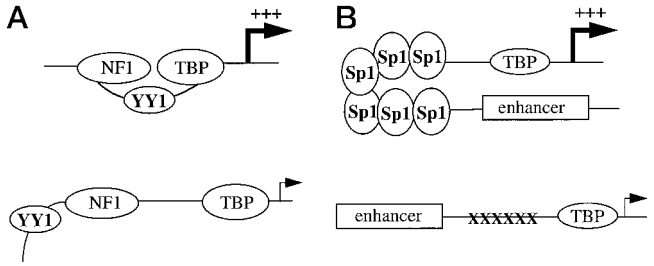

FIG. 1. **Transcription factor-induced DNA bending can influence promoter activity.** *A,* DNA bending induced by a properly positioned YY1 protein brings NF1 closer to the basal transcription complex (*e.g.* TBP); placement of YY1 upstream of NF1 abolishes YY1-mediated activation. *B,* Sp1-mediated DNA bending at the SV40 early promoter brings the enhancer closer to the basal promoter complex; mutation of the Sp1 sites (indicated by the *X*s) reduces DNA bending and transcriptional activation.

Consensus	Overlapping Site	Promoter
Sp1: GGG GCG GGG Egr:GCG GGG GCG	Sp1 GGGGCGTGGGCTG Egr	mdr1
E2F: TTTSSCGC CDE: CCGCS (S=G or C)	E2F TCT CCC GCC CDE	B-myb
SRE: CC(A/T)6GG YY1: CCATNTT	SRE CCA TAT TTG G YY1	skeletal α-actin

FIG. 2. **Overlapping binding sites can influence the response to a transcriptional activator.** Overlapping binding sites for Sp1 and Egr, E2F and CDF-1 (*CDE*), and YY1 and SRF (*SRE*) can result in competitive binding. Therefore, the contribution of sequences flanking a binding site can be important in determining the function of a factor at a particular promoter.

influence the transcriptional activity of specific promoters. For example, the T-cell receptor α (TCRα) enhancer contains a LEF-1 site flanked on either side by a CREB and an Ets-binding site; activation of the TCRα enhancer requires proteins that bind all three sites (7). Increasing the spacing between the LEF-1 site and either the Ets or CREB site reduces transcriptional activation, suggesting that the precise distance between the sites is critical. These studies led to the hypothesis that DNA bending caused by LEF-1 promotes interactions between the proteins bound to the CREB and Ets sites. In support of this model, further studies showed that placing the Ets and CREB sites next to each other abrogates the need for LEF-1 (7). Also, studies using variant LEF-1-binding sites show a correlation between the extent of DNA bending and transcriptional activation of the TCRα enhancer, supporting the hypothesis that LEF-1-induced DNA bending contributes to promoter activity (8).

Sp1 can also achieve context-dependent transcriptional activation by altering the structure of DNA. The simian virus 40 (SV40) early promoter is composed of three 21-base pair repeats, with each repeat containing two binding sites for Sp1. Robust transcriptional activity from this promoter also requires an upstream enhancer that binds a number of different transcription factors. The 21-base pair repeats contain an intrinsic DNA bend that can be stabilized by binding of Sp1 (9). It has been proposed that Sp1-stabilized bending activates transcription by bringing the factors bound to the upstream enhancer closer to the basal promoter (Fig. 1*B*). Another study has also documented the ability of Sp1 to alter the structure of DNA. Courey *et al.* (10) demonstrated that Sp1 proteins bound 1.8 kilobases downstream of a promoter can cooperate with Sp1 bound at the basal promoter region to synergistically activate transcription. The proximally and distally bound Sp1 proteins can physically interact to form a looped DNA structure (11). Therefore, one function of Sp1 appears to be the alteration of DNA structure, resulting in the recruitment of distally bound activators to a position more proximal to the basal transcription complex.

Overlapping Binding Sites Can Influence the Response to a Transcriptional Activator—The presence of overlapping transcription factor binding sites often makes it difficult to determine which factor is mediating transcriptional regulation (Fig. 2). At many promoters, Sp1 sites overlap with binding sites for the early growth response (Egr) family of GC-rich DNA-binding transcription factors; binding of Sp1 and Egr1 is often mutually exclusive. A GC-rich region containing overlapping Sp1 and Egr sites is responsible for phorbol 12-myristate 13-acetate (PMA)-induced transcription of the platelet-derived growth factor A-chain promoter (12). Although both proteins can bind to the GC-rich element, mutational analyses demonstrated that Egr1, not Sp1, is responsible for PMA-induced activation of the promoter. Sp1 binding to an overlapping Sp1/Egr site is required for v-Raf-mediated activation of the multidrug resistance gene 1 transcription in quiescent NIH 3T3 cells (13). In contrast, Egr1 mediates the activation of multidrug resistance gene 1 transcription by 12-*O*-tetradecanoylphorbol-13-acetate in K562 cells through the same Sp1/Egr1 element (14). Thus, Sp1 and Egr1 can differentially regulate transcription through the same binding sites, depending on the cellular environment.

The role of E2F in the regulation of several promoters is influenced by an overlapping binding site for the transcriptional repressor protein, CDE-CHR binding factor-1 (CDF-1). Transcription from the B-myb and cyclin A promoters, both of which contain overlapping E2F and CDF-1 sites, is repressed in the G_0 phase of the cell cycle. Mutational analyses indicated that the E2F site is necessary for repression of the B-*myb* promoter (15). The B-*myb* promoter strongly binds E2F4, the predominant E2F protein in G_0 phase cells, and only weakly binds CDF-1. In contrast, CDF-1 binding, but not E2F binding, is critical for repression of the cyclin A promoter (16), suggesting that CDF-1 mediates this G_0 phase repression. In support of this hypothesis, the cyclin A promoter is only weakly bound by E2F4 (16).

YY1 has been shown to repress certain promoters because of the arrangement of overlapping binding sites. For example, YY1 and serum response factor (SRF) bind to the serum response element (SRE) of the skeletal α-actin promoter in a mutually exclusive manner (17, 18). Normally, YY1 blocks access of SRF and prevents activation of the promoter. However, under conditions in which YY1 DNA binding activity decreases (*e.g.* during myogenic differentiation), SRF has free access to its binding site, and transcription from the skeletal α-actin promoter is increased. The SRE in the c-*fos* promoter is also bound by both YY1 and SRF (19). The binding of these two factors in primary chicken muscle cells is mutually exclusive, and YY1 can block the SRF-mediated induction of the c-*fos* promoter. Thus, removal of a YY1 site (CCATNTT) from within an SRE ($CC(A/T)_6GG$) can result in a misunderstanding of the role of YY1 in the regulation of a particular gene.

Promoter-specific Protein-Protein Interactions Can Influence the Response to a Transcriptional Activator—Cooperative interactions between Sp1 and other DNA-bound transcription factors can result in context-dependent transcriptional regulation. Mutational analyses of the human immunodeficiency virus (HIV-1) enhancer indicated that adjacent binding sites for the nuclear factor of the κ light chain enhancer in B cells (NF-κB) and Sp1 are sufficient to direct mitogen-stimulated transcription (20). However, mutation of either the NF-κB or the Sp1 site or the addition of 5 base pairs between the two sites abolishes activation and binding of both proteins. These studies demonstrate that a protein-protein interaction between NF-κB and Sp1 can result in cooperative DNA binding and synergistic activation of promoters containing appropriately spaced binding sites. A protein-protein interaction between Sp1 and the octamer-binding transcription factor (OTF-1/Oct-1) mediates transcriptional activation of the upstream U2 small nuclear RNA gene enhancer (21, 22). Sp1 and OTF-1/Oct-1 cooperate in DNA binding and synergistic activation, both of which become more pronounced when the Sp1 site is combined with a low affinity OTF-1/Oct-1-binding site (Fig. 3*A*). The cooperativity between OTF-1/Oct-1 and Sp1 is distance-dependent; the addition of only 15 base pairs between the Sp1 site and a low affinity OTF-1/Oct-1 site reduced activation 5-fold. The erythroid-specific GATA binding factor (GATA) family of transcriptional activators can also synergize with Sp1 at the erythroid pyruvate kinase and glycophorin B

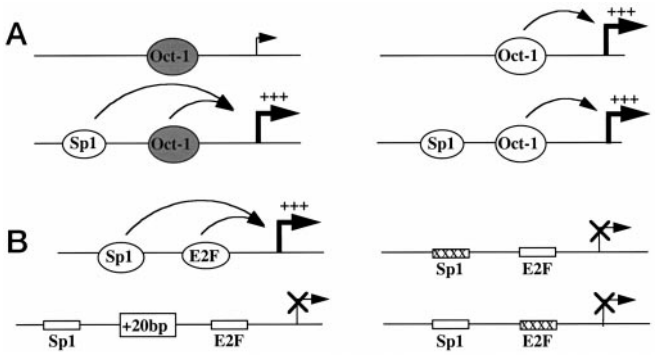

FIG. 3. **Promoter-specific protein-protein interactions can influence the response to a transcriptional activator.** *A,* synergy with Sp1 is needed for robust activation of a U2 small nuclear RNA enhancer containing a low affinity Oct-1 site (indicated by the *gray shading*); a high affinity Oct-1 site does not require synergy with Sp1. *B,* E2F can synergize with Sp1 in activation of the murine *tk* promoter. However, insertion of 20 base pairs between the two sites or mutation of either the Sp1 or the E2F site results in loss of binding of both factors and loss of activation.

promoters (23). In contrast, Sp1 and GATA do not synergize at a β^{maj}-globin-derived promoter, although it contains similarly spaced Sp1 and GATA sites. The exact promoter features that specify GATA and Sp1 cooperativity have not yet been determined. Taken together, these results clearly show that the presence of other site-specific DNA-binding proteins can greatly influence the ability of Sp1 to activate transcription.

The ability of LEF-1 protein-protein interactions to influence transcription is also promoter-specific because of the interaction of LEF-1 with two different coactivators, β-catenin and ally of LEF-1 (ALY). Each of these coactivators enhances the ability of LEF-1 to activate a specific subset of promoters (24, 25). For example, multimerized LEF-1 sites cloned upstream of the c-*fos* minimal promoter can confer robust activation by LEF-1·β-catenin complexes, but this same promoter construct is not responsive to LEF-1·ALY complexes. In contrast, the TCRα enhancer is highly responsive to LEF-1·ALY complexes but cannot be activated by LEF-1·β-catenin complexes. The circumstances that determine the ability of LEF-1·coactivator complexes to activate some, but not all, promoters are not yet understood but appear to be promoter context-dependent.

Several studies have examined functional interactions between E2F and other DNA-bound transcriptional activators. For example, E2F and Sp1 have been shown to cooperate in activation of the murine thymidine kinase (*tk*) promoter (Fig. 3*B*). Insertion of 20 base pairs between adjacent Sp1- and E2F-binding sites abolishes *tk* promoter activity, and mutation of either site eliminates binding of both Sp1 and E2F, demonstrating that these activators cooperate in DNA binding. Sp1 can bind to the N-terminal region of E2F1, E2F2, and E2F3, but not to E2F4 or E2F5, suggesting that cooperativity with Sp1 may be limited to a subset of E2F proteins (26, 27). In support of this hypothesis, Lin *et al.* (27) have shown that E2F1, but not E2F4, can synergize with Sp1 in activation of the hamster dihydrofolate reductase and human DNA polymerase α promoters. Furthermore, E2F1 can synergize with Sp1, but not Sp3, in activation of the c-*myc* promoter (28), suggesting that cooperativity is also limited to a subset of the Sp1 family of proteins. Additional studies have shown that YY1 and the CCAAT-binding factor NF-Y can also cooperate with E2F to mediate growth-regulated transcription (29). In fact, many E2F-regulated promoters contain Sp1, YY1, and/or NF-Y binding sites, suggesting a great potential for context-dependent E2F activities.

The Structure of the Core Promoter Can Influence the Response to a Transcriptional Activator—TATA boxes and initiators (Inrs) are core promoter elements that mediate formation of a transcription complex containing RNA polymerase II and other general transcription factors. Emami *et al.* (30) found that Sp1 exhibited a strong preference for promoters containing the terminal deoxynucleotidyltransferase (TdT) promoter Inr element and that the addition of a TATA box had only modest effects on activation (Fig. 4). Furthermore, a truncated Sp1 protein containing only the glutamine-rich activation domains exhibited a strict dependence on the Inr element. Not all activators show this same preference; *e.g.*

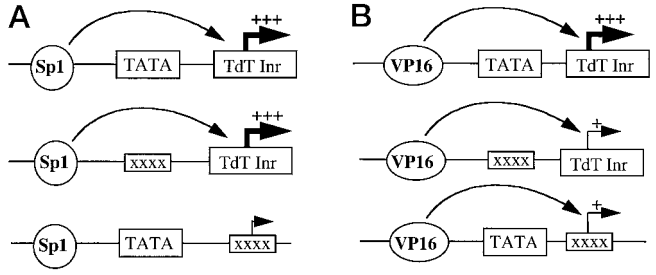

FIG. 4. **The structure of the core promoter can influence the response to a transcriptional activator.** *A,* core promoters containing the TdT Inr can be activated by Sp1, regardless of the presence of a TATA box. However, mutation of the Inr greatly reduces activation by Sp1. In contrast, VP16 can efficiently activate all core promoters but shows maximal activation of core promoters containing both an Inr and a TATA box.

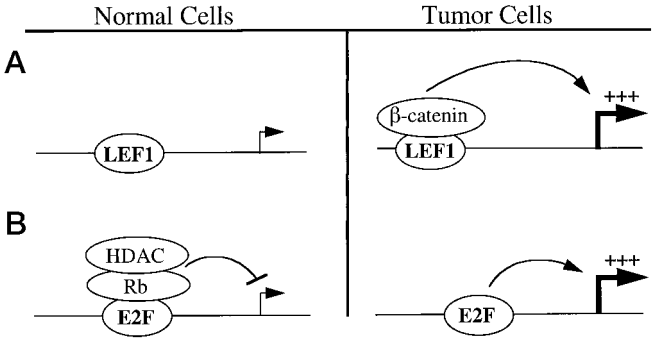

FIG. 5. **The cellular environment can influence the response to a transcriptional activator.** *A,* the loss of the APC tumor suppressor protein in colon cancer cells causes an increase in β-catenin·LEF-1 complexes and activation of LEF-1 target genes. *B,* the loss of the Rb tumor suppressor protein in many types of tumor cells can result in the switch of E2F function from a repressor to an activator, resulting in constitutive activation of E2F target genes. *HDAC,* histone deacetylases.

the herpes simplex virus virion protein 16 (VP16) shows a preference for core promoters that contain both a TATA box and an Inr (Fig. 4) (30), whereas the upstream stimulatory factor shows a strong preference for a TATA box (31). A TATA box is a binding site for TBP, one component of the general transcription factor TFIID. The fact that Sp1 can activate transcription independently of a TATA box suggests that Sp1 and the TATA box may provide mechanistically redundant functions. In support of this hypothesis, Sp1 has been shown to activate transcription by contacting $TAF_{II}130$, another subunit of TFIID (32).

In addition to its role as an upstream activator or repressor of transcription, YY1 can also serve as an initiator binding protein, most likely because of its ability to directly recruit TFIIB and RNA polymerase II (33, 34). However, the levels of YY1-mediated transcription that are observed in the absence of upstream factors are quite low. The addition of an Sp1-binding site upstream of the YY1-binding Inr of the adeno-associated virus P5 (AAV P5) promoter results in a marked increase in promoter activity (33). This synergy between YY1 and Sp1 could result from a physical interaction between the two proteins (35) or the ability of Sp1 to recruit TFIID (32). Although Sp1 appears to function in concert with a variety of initiator elements (TdT and AAV P5), it cannot activate transcription in combination with all Inr elements. The hamster *cad* promoter contains two Sp1-binding sites located upstream of a consensus Inr. Replacement of the *cad* Inr with two other consensus Inr sequences resulted in robust transcriptional activity of one construct, but not the other (36), suggesting that Sp1 can functionally synergize with some, but not all, initiator binding proteins.

The Cellular Environment Can Influence the Response to a Transcriptional Activator—The loss of tumor suppressor genes and/or the increase in amount of oncogenic transcription factors can affect the degree to which a site-specific transcription factor can regulate gene expression. For example, the transcriptional activity of LEF-1 can vary in different cells because of changes in the subcellular localization of β-catenin (Fig. 5*A*). LEF-1, which does not contain an activation domain, cannot stimulate transcription from multiple

binding sites cloned upstream of a minimal promoter. However, LEF-1·β-catenin complexes can stimulate transcription because of a transcriptional activation domain in β-catenin (24). β-Catenin is normally found in the cytoplasm complexed with the adenomatous polyposis coli (APC) protein. Mutations in APC (found in a large percentage of colon cancer cells) result in disruption of the complex, allowing β-catenin to translocate to the nucleus and bind to TCF/LEF-1 proteins (37, 38). Thus, certain LEF target genes, such as c-*myc*, are only activated by LEF family members in tumor cells that contain high levels of nuclear β-catenin (39).

For many E2F target genes, including *E2F1* and B-*myb*, E2F functions mainly as a transcriptional repressor because of the formation of a complex with hypophosphorylated Rb and associated histone deacetylases (4). However, in many tumor cells, Rb is either lost or hyperphosphorylated, rendering it nonfunctional. This loss of the repression component of the E2F complex can result in a switch from E2F-mediated repression to E2F-mediated activation of target genes (Fig. 5*B*). For example, malignant gliomas, which commonly have mutations in the Rb signaling pathway, show increased E2F1 promoter activity, as compared with normal brain tissue (40). Mutational analyses indicated that E2F functions as an activator of the *E2F1* promoter in these tumor cells. Similarly, others have shown that the E2F-binding site in the B-*myb* promoter is converted to a positive element in F9 embryonal carcinoma cells, which contain high levels of free E2F (41).

The activity of YY1 can also be influenced by the cellular environment. For example, the c-Myc protein can associate with YY1 and inhibit both its transcriptional activation and repression properties (42). In cells containing low amounts of c-Myc, such as quiescent 3T3 fibroblasts, YY1 is free to regulate transcription (43). In contrast, after mitogenic stimulation of 3T3 cells, levels of c-Myc increase and YY1 is recruited into a c-Myc·YY1 complex. Although the c-Myc·YY1 complex can bind to YY1 sites, it does not possess transcriptional regulatory activity. This suggests that in tumor cells which contain high levels of c-Myc, such as Burkitt's lymphomas, YY1 may not be able to activate or repress transcription.

Conclusions

We have provided examples that highlight the importance of studying the function of transcription factors in a natural promoter context. For instance, the transfer of a binding site for a protein that induces DNA bending from its position in a natural promoter to a random position in a synthetic promoter can result in a misinterpretation of the role of that factor in transcriptional regulation (Fig. 1). The presence of overlapping transcription factor binding sites at a promoter can also result in context-specific regulation (Fig. 2). Therefore, determination of the function of a protein at a particular promoter requires consideration of the sequences flanking the binding sites. The ability of a transcription factor to function as an activator or repressor of transcription and the degree to which a promoter responds to a factor can also vary depending upon the presence of other site-specific transcription factors (Fig. 3). Some upstream activators cooperate with specific core promoter elements to provide robust transcriptional activation (Fig. 4). Finally, transcriptional activity can clearly be influenced by the cellular environment in which the assays are performed (Fig. 5). We believe that the five mechanisms described in this review provide general models that are applicable to many site-specific transcriptional regulators. In conclusion, we suggest that, to the greatest extent possible, the function of a transcription factor-binding site should be studied in the context of a natural promoter and in cells that are most physiologically relevant to the hypothesis being tested.

REFERENCES

1. Shi, Y., Lee, J.-S., and Galvin, K. M. (1997) *Biochim. Biophys. Acta* **1332,** F49–F66
2. Bienz, M. (1998) *Curr. Opin. Cell Biol.* **10,** 366–372
3. Lania, L., Majello, B., and De Luca, P. (1997) *Int. J. Biochem. Cell Biol.* **29,** 1313–1323
4. Dyson, N. (1998) *Genes Dev.* **12,** 2245–2262
5. Kim, J., and Shapiro, D. J. (1996) *Nucleic Acids Res.* **24,** 4341–4348
6. Natesan, S., and Gilman, M. Z. (1993) *Genes Dev.* **7,** 2497–2509
7. Giese, K., and Grosschedl, R. (1993) *EMBO J.* **12,** 4667–4676
8. Giese, K., Pagel, J., and Grosschedl, R. (1997) *Proc. Natl. Acad. Sci. U. S. A.* **94,** 12845–12850
9. Sun, D., and Hurley, L. H. (1994) *Biochemistry* **33,** 9578–9587
10. Courey, A. J., Holtzman, D. A., Jackson, S. P., and Tjian, R. (1989) *Cell* **59,** 827–836
11. Su, W., Jackson, S., Tjian, R., and Echols, H. (1991) *Genes Dev.* **5,** 820–826
12. Khachigian, L. M., Williams, A. J., and Collins, T. (1995) *J. Biol. Chem.* **270,** 27679–27686
13. Miltenberger, R. J., Farnham, P. J., Smith, D. E., Stommel, J. M., and Cornwell, M. M. (1995) *Cell Growth Differ.* **6,** 549–556
14. McCoy, C., Smith, D. E., and Cornwell, M. M. (1995) *Mol. Cell. Biol.* **15,** 6100–6108
15. Lucibello, F. C., Liu, N., Zwicker, J., Gross, C., and Muller, R. (1997) *Nucleic Acids Res.* **25,** 4921–4925
16. Liu, N., Lucibello, F. C., Engeland, K., and Muller, R. (1998) *Oncogene* **16,** 2957–2963
17. Lee, T.-C., Chow, K.-L., Fang, P., and Schwartz, R. J. (1991) *Mol. Cell. Biol.* **11,** 5090–5100
18. Lee, T.-C., Shi, Y., and Schwartz, R. J. (1992) *Proc. Natl. Acad. Sci. U. S. A.* **89,** 9814–9818
19. Gualberto, A., LePage, D., Pons, G., Mader, S. L., Park, K., Atchison, M. L., and Walsh, K. (1992) *Mol. Cell. Biol.* **12,** 4209–4214
20. Perkins, N. D., Edwards, N. L., Duckett, C. S., Agranoff, A. B., Schmid, R. M., and Nabel, G. J. (1993) *EMBO J.* **12,** 3551–3558
21. Strom, A. C., Forsberg, M., Lillhager, P., and Westin, G. (1996) *Nucleic Acids Res.* **24,** 1981–1986
22. Janson, L., and Pettersson, U. (1990) *Proc. Natl. Acad. Sci. U. S. A.* **87,** 4732–4736
23. Gregory, R. C., Taxman, D. J., Seshasayee, D., Kensinger, M. H., Bieker, J. J., and Woychowski, D. M. (1996) *Blood* **87,** 1793–1801
24. Hsu, S.-C., Galceran, J., and Grosschedl, R. (1998) *Mol. Cell. Biol.* **18,** 4807–4818
25. Bruhn, L., Munnerlyn, A., and Grosschedl, R. (1997) *Genes Dev.* **11,** 640–653
26. Karlseder, J., Rotheneder, H., and Wintersberger, E. (1996) *Mol. Cell. Biol.* **16,** 1659–1667
27. Lin, S.-Y., Black, A. R., Kostic, D., Pajovic, S., Hoover, C. N., and Azizkhan, J. C. (1996) *Mol. Cell. Biol.* **16,** 1668–1675
28. Majello, B., De Luca, P., Suske, G., and Lania, L. (1995) *Oncogene* **10,** 1841–1848
29. van Ginkel, P. R., Hsiao, K.-M., Schjerven, H., and Farnham, P. J. (1997) *J. Biol. Chem.* **272,** 18367–18374
30. Emami, K. H., Navarre, W. W., and Smale, S. T. (1995) *Mol. Cell. Biol.* **15,** 5906–5916
31. Luo, X., and Sawadogo, M. (1996) *Mol. Cell. Biol.* **16,** 1367–1375
32. Saluja, D., Vassallo, M. F., and Tanese, N. (1998) *Mol. Cell. Biol.* **18,** 5734–5743
33. Seto, E., Shi, Y., and Shenk, T. (1991) *Nature* **354,** 241–245
34. Usheva, A., and Shenk, T. (1996) *Proc. Natl. Acad. Sci. U. S. A.* **93,** 13571–13576
35. Lee, J.-S., Galvin, K. M., and Shi, Y. (1993) *Proc. Natl. Acad. Sci. U. S. A.* **90,** 6145–6149
36. Kollmar, R., Sukow, K. A., Sponagle, S. K., and Farnham, P. J. (1994) *J. Biol. Chem.* **269,** 2252–2257
37. Morin, P. J., Sparks, A. B., Korinek, V., Barker, N., Clevers, H., Vogelstein, B., and Kinzler, K. W. (1997) *Science* **275,** 1787–1790
38. Korinek, V., Barker, N., Morin, P. J., van Wichen, D., de Weger, R., Kinzler, K. W., Vogelstein, B., and Clevers, H. (1997) *Science* **275,** 1784–1787
39. He, T.-C., Sparks, A. B., Rago, C., Hermeking, H., Zawel, L., da Costa, L. T., Morin, P. J., Vogelstein, B., and Kinzler, K. W. (1998) *Science* **281,** 1509–1512
40. Parr, M. J., Manome, Y., Tanaka, T., Wen, P., Kufe, D. W., Kaelin, W. G. J., and Fine, H. A. (1997) *Nat. Med.* **3,** 1145–1149
41. Bennett, J. D., Farlie, P. G., and Watson, R. J. (1996) *Oncogene* **13,** 1073–1082
42. Shrivastava, A., Saleque, S., Kaplana, G. V., Artandi, S., Goff, S. P., and Calame, K. (1993) *Science* **262,** 1889–1892
43. Shrivastava, A., Yu, J., Artandi, S., and Calame, K. (1996) *Proc. Natl. Acad. Sci. U. S. A.* **93,** 10638–10641