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Minireview

How do eukaryotic activator proteins stimulate the rate of transcription by RNA polymerase II?

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A large number of activator proteins have now been identified in higher and lower eukaryotes, which bind to the regulatory regions of protein-encoding genes and increase the rate at which they are transcribed by RNA polymerase II. The mechanism by which activators function is being intensively studied and some of the targets of transcriptional activation domains have now been identified. These studies have also revealed novel classes of regulatory factors, which were not anticipated by extrapolating from the principles obtained with prokaryotic promoters.

Activator; RNA polymerase II; Mechanism of activation; General transcription factor; Coactivator

1. INTRODUCTION

A major goal in the field of eukaryotic gene regulation is to understand how the activator proteins that bind to the upstream promoter elements and enhancers of RNA polymerase II-dependent genes stimulate the rate at which these genes are transcribed. RNA polymerase II is unable to recognize promoters on its own and is assisted by a number of accessory proteins, referred to as the general transcription factors. A simple hypothesis is that transcriptional activators directly interact with either RNA polymerase II or one or more of the general transcription factors, and thereby stimulate the rate of formation or activity of the transcription initiation complex or increase the number of complexes formed (see [1] for a discussion of this and alternative ideas). Here, we will discuss the results of a number of experiments that have attempted to identify the targets of transcriptional activation domains. However, it is important to recall that eukaryotic genes are associated with histones in vivo, which have been found to exclude the general transcription factors from the promoter both in vivo and in vitro and which appear to have a repressive effect on transcription. Therefore activator proteins might also stimulate transcription by altering chromatin structure so as to make the promoter accessible to RNA polymerase II and its associated factors. Evidence in favour of this hypothesis has recently been reviewed elsewhere [2].

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2. THE TRANSCRIPTION INITIATION COMPLEX

The region of a promoter in which the RNA polymerase II transcription initiation complex is assembled and where transcription initiates is known as the core or minimal promoter (Fig. 1). Usually this contains a TATA box sequence [3], which specifies the direction of transcription and the site of initiation, and which will allow a basal level of transcription in vitro. In addition to the TATA box, or as an alternative, some core promoters contain sequences around the initiation site (initiators) which can also direct the assembly of an initiation complex (see [4]). The general transcription factors were originally defined as factors necessary for the in vitro transcription of core promoters by RNA polymerase II, and were thought to be required by all promoters. General transcription factors were identified by chromatographically fractionating extracts prepared from cell lines or tissues and testing the importance of particular fractions for transcription in vitro. Most of the general transcription factors have now been purified to homogeneity and cDNAs encoding the polypeptides associated with particular activities have been isolated (see [5,6] and Table I.

The transcription initiation complex is assembled in a temporally ordered fashion [21–23]. The first event is the binding of TFIID to the TATA box sequence. In contrast to many activator proteins, TFIID binds slowly to the promoter, but once formed, the TFIID–TATA box complex is very stable (see [24] for refs.). The binding of TFIID is facilitated by another factor, TFIIA, which is unable to bind to the promoter on its

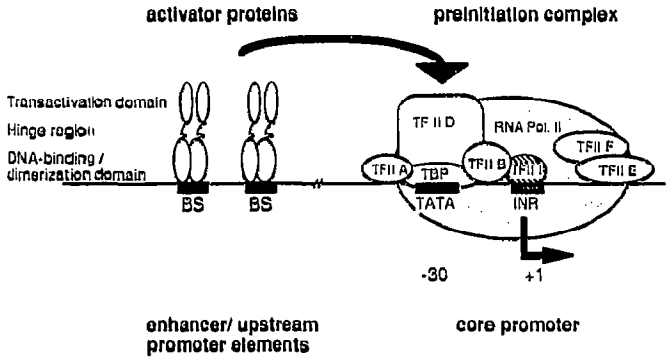

Fig. 1. Model of the RNA-polymerase II preinitiation complex on a typical eukaryotic promoter. The binding of the TATA-box binding protein (TBP), which is part of TFIID, to the TATA box (consensus $TATA^{A}/_{T}A$) is stabilized by TFIIA in a promoter without an initiator (INR) element at the +1 position. The subsequent assembly of TFIIB, followed by the RNA-polymerase, which is associated with TFIIE and TFIIF creates an active preinitiation complex (PIC). In a promoter containing INR sequences (consensus YAYTCYYY, where Y=pyrimidine), TFII-I is able to substitute for TFIIA, indicating alternative pathways for PIC formation, whereas in a TATA-less promoter, TFII-I is necessary for TFIID binding. The assembly of the PIC might be facilitated by the action of transcriptional transactivator proteins. They usually bind as homodimers to their binding sites (BS) located upstream (or downstream) of the TATA-box and might activate transcription by contacting one or more of the general transcription factors. Activator proteins are composed of distinct domains, a DNA-binding and dimerization domain and a transactivation domain, which may be separated by a hinge region. Some activators do not bind to specific DNA sequences and recognize the promoter by interacting with other transcription factors already bound to the DNA e.g. VP16 interacts with OCT1 and E1a binds to ATF.

own. Once the D–A complex is formed, TFIIB binds to the promoter downstream of the TATA box over the initiation site. The D–A–B complex is then recognized by RNA polymerase II in association with TFIIE and TFIIF. This complex is functionally analogous to the prokaryotic closed complex. Transcription initiation requires hydrolysis of ATP and leads to melting of promoter DNA and open complex formation [25] followed by mRNA initiation and elongation. In theory, any of the steps in the assembly of the preinitiation complex could be rate limiting on a particular promoter in vivo and might be a target for transcriptional activator proteins. Originally the general transcription factors were thought to be required by all polymerase II promoters. However, the situation is probably more complex than this. For example, a new factor has been isolated, TFII-I, which binds to the initiator and can functionally replace TFIIA [20]. However, it can only be used by promoters that contain initiator elements. Similarly, whilst TFIIE is essential for transcription of the adenovirus major late promoter in vitro it is apparently not required for the immunoglobulin heavy chain core promoter, which in turn requires two novel activities referred to as 700 kDa and 90 kDa [26].

3. TFIID AND TFIIB AS TARGETS OF ACTIVATION DOMAINS

3.1. *The importance of TFIID*

TFIID has attracted considerable attention as a potential target for transcriptional activators, since it appears to play a crucial role in the assembly of the transcription initiation complex on all promoters tested so far in vitro. In the case of core promoters with a TATA box, TFIID is the only general transcription factor which can specifically recognize the promoter on its own. The binding of TFIIB, Pol II, TFIIE and TFIIF depends on the prior formation of a TFIID–TATA box complex (see, for example, [22]). Promoters which contain an initiator sequence but not a TATA box also require TFIID [27,28], which may be recruited to the promoter by means of a direct interaction with TFII-I [6].

A number of early studies either showed that activator proteins could alter the binding of TFIID to the promoter (USF:[29]; GAL4 derivatives: [30]; ATF: [31]) or implicated TFIID as a target (pseudo rabies virus IE protein: [32]). However, all of these experiments were performed with partially purified TFIID and therefore it could not be excluded that the activators interacted with other proteins in the TFIID fraction. Subsequent work has shown that TFIID is in fact a large multiprotein complex consisting of a TATA box-binding protein (TBP) and a variable number of associated polypeptides referred to as TAFs (TBP associated factors; reviewed in [33]). The TBP has now been cloned from several species (reviewed in [34]) and its structure is shown in Fig. 2. Recombinant TBP can efficiently bind to the TATA box on its own and will support basal transcription of a core promoter in vitro when mixed with the other general transcription factors. Is there any evidence to suggest that activators directly interact with the TBP?

3.2. *The VP16 activator*

The VP16 protein of herpes simplex virus 1 contains a transactivation domain rich in acidic amino acid residues, and is one of the best-characterized eukaryotic activator proteins (see, for example [35]). In contrast to many other transcription factors VP16 does not bind to a specific DNA sequence and recognizes the promoter by interacting with another factor (OCT1) already bound to the DNA. Stringer et al. [36] first showed that both the TFIID activity in HeLa cell nuclear extracts and recombinant yeast TBP could specifically bind to columns containing agarose beads linked to a fusion between protein A and the transactivation domain of VP16. However, since the TBP is relatively basic and the VP16 activation domain is highly acidic, it was necessary to show that binding was not the result of a non-specific ionic interaction. The same group therefore tested the yeast TBP on columns prepared from mutant

VP16 proteins with reduced transcriptional activity [37]. Cress and Triezenberg [35] had previously shown that a particular phenylalanine residue in the VP16 activation domain (Phe-442) plays a critical role in transactivation. Ingles et al. [37] found that changing Phe-442 in the protein A–VP16 fusion proteins to other residues, which did not alter the overall charge of VP16, reduced the binding of the TBP by a degree comparable to the effect of these mutations on transactivation in vivo suggesting that the interaction was specific. However, mutation of acidic residues in VP16 had a more severe effect on TBP binding in vitro than on activation in vivo.

At the same time Lin and Green [38] showed that a chimaeric activator consisting of the GAL4 DNA binding domain fused to an amphipathic α-helix rich in acidic residues stimulated transcription in vitro by recruiting TFIIB to the initiation complex, rather than TFIID. Furthermore, they found that both TFIID and TFIIB bound to a glutathione-*S*-transferase (GST)–VP16 column in buffer containing 0.1 M KCl, but when a buffer containing 0.2 M KCl was used only TFIIB was bound. This binding was abolished by mutating Phe-442 in VP16 to proline. Recombinant TFIIB expressed in *E. coli* could also interact with a GST–VP16 column, proving that the interaction was direct [39]. Taken together, these results suggest that the acidic VP16 activation domain can interact with both TFIID and TFIIB in vitro but that the latter protein is bound more strongly.

3.3. *Interactions between other activators and the TBP*

Like VP16, the 13S adenovirus E1 a protein is a potent activator which does not have a specific DNA binding site. It does not contain an acidic activation domain but has also been shown to interact directly with the TBP [40,41]. In these studies, the interaction was demonstrated in vitro by a variety of techniques: E1a affinity chromatography, protein–protein blotting, sedimentation velocity centrifugation of E1a–TBP complexes and co-immunoprecipitation. E1a–TBP complexes were also immunoprecipitated from cell extracts, although it was necessary to use cells infected with recombinant vaccinia viruses overexpressing E1a and the TBP. The 12S E1a protein, which is a less potent transactivator than the 13S form, bound the TBP more weakly. Similar approaches have been used to demonstrate that the Epstein-Barr virus Zta protein, which has an activation domain different to those of VP16 and E1a, can also directly interact with the TBP in vitro [42]. Finally, in our laboratory we have found that the bovine papillomavirus 1 E2 protein and the TBP bind cooperatively to an oligonucleotide containing an E2 site 8 bp from a TATA box in gel retardation assays, suggesting that E2 may also interact directly with the TBP [43].

In summary, a number of activators, some of which bind to specific DNA sequences (Zta and E2) and some of which recognize target genes by interacting with other transcription factors (VP16 and E1a), appear to interact directly with the TBP in vitro. What regions of the TBP are contacted? The DNA binding domain of the TBP contains a repeat of basic amino acid residues, which are predicted to fall on the same face of an α-helix. It is interesting to note that TFIIB also contains a similar basic repeat (Fig. 2). Point mutation of these residues in the TBP has shown that they are not required for DNA binding [44] but that they are important for interaction with TFIIA [45]. It is tempting to speculate that the basic residues might also be involved in direct interactions with activators. In fact E1a has

Table I

General transcription initiation factors

Factor	Polypeptide composition	Function
TFIIA	Yeast: 2 subunits: 32 kDa (TOA1) 13.5 kDa (TOA2) [7] Human: Trimer of 34, 19 and 14 kDa [8]	Stabilizes the binding of TBP to the TATA-box: not essential for all promoters [22]
TFIIB	Yeast: 38 kDa [9] Human: 33 kDa [10,11]	promotes binding of RNA-pol. II; target of transcriptional transactivator proteins (VP 16) [38] yTFIIB: required for start site selection
TFIID	multiprotein complex >100 kDa composed of TAFs. TBP (38 kDa) (see [33,34])	TBP: binding to the TATA-box, initial step in PIC assembly, target of transactivator proteins
TFIIE	Human: tetramer, composed of two 57 kDa and two 34 kDa subunits [12–14]	RNA pol. associated factor (RAP)
TFIIF	Human: tetramer with two 74 kDa [15,16] and two 30 kDa subunits [17]	small subunit interacts with RNA pol. II, suppresses binding of RNA pol. II to non-promoter DNA, enables pol. II to be recruited to the D–A–B complex together with TFIIE [18,19]
TFII I	Human: 120 kDa	binds to the INR-element, promotes TBP binding [6,20]

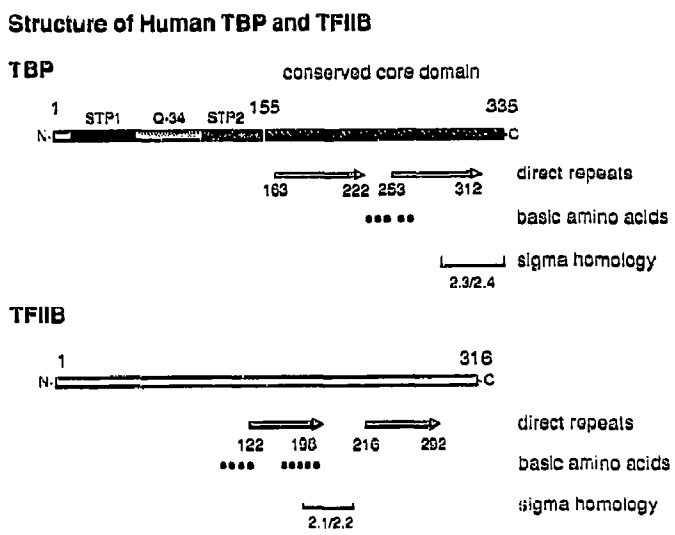

Fig. 2. Similarity in structural features between the human TATA-binding protein (TBP) and TFIIB. The carboxy-terminal 180 amino acids of the TBP are sufficient for DNA-binding and basal transcription and are evolutionarily conserved (e.g. there is 81% identity between the human and budding yeast TBPs). The TBP core domain contains two direct repeats of 59 amino acids important for DNA-binding. A repeat of basic amino acids with the potential to form an α-helix with the basic residues on one face is not required for DNA-binding, but might interact with certain types of activator proteins. A region which shows homology to the subregions 2.3 and 2.4 of the σ^{70} factor of *E. coli* is indicated. The non-conserved amino-terminus of the human TBP is composed of a region with 34 glutamines (Q-34), flanked by two regions (STP1 and STP2) rich in serines (S), threonines (T) and prolines (P), which might serve as interfaces for intermolecular protein–protein interactions. Human TFIIB contains similar structural motifs to those in the TBP, suggesting that they may have related functions. Two direct repeats of 76 amino acids, two repeats of basic amino acids and a sequence, which is related to the σ^{70} factor 2.1/2.2 region are indicated.

been shown to bind to fusion proteins containing residues 221–271 of the TBP, a region which contains the basic repeat [41]. However, the Zta–TBP interaction appears to require sequences C-terminal to this region [42] suggesting that different activation domains may contact the TBP in different places.

4. THE ROLE OF COACTIVATORS

4.1 *Definition of coactivators*

Initial studies with purified recombinant human or *Drosophila* TBP showed that whilst they could efficiently participate in the basal transcription of core promoters in vitro they did not allow activation by the mammalian transcription factors SP1 or USF, whereas TFIID partially purified from HeLa cells or *Drosophila* embryos did [46–48]. This suggested that other polypeptides in the TFIID complex (the TAFs) play an important role in the process of transcriptional activation and these were therefore named coactivators. This hypothesis was recently confirmed by using urea to separate the TAFs from the TBP in the *Drosophila* TFIID complex. The TBP obtained in this way was unable to mediate activation by SP1 or the *Drosophila* activator NTF-1, but addition of the renatured TAF fraction restored the activator response [49]. When the *Drosophila* TFIID complex was immunoprecipitated with an anti-TBP antibody six major polypeptides co-precipitated. Similar results were obtained with human TFIID [50]. In parallel with these studies a 'mediator' activity, distinct from the general transcription factors, was purified from yeast cells and shown to be necessary for the acidic activators GAL4–VP16 and GCN4 to be able to function efficiently in a reconstituted in vitro system [51,52]. A similar activity, which allows transcriptional stimulation by GAL4–VP16 in a reconstituted mammalian system, has been isolated from HeLa cell extracts [53].

4.2. *Mechanism of action coactivators*

Exactly how coactivators/mediators facilitate transcriptional activation by activator proteins is unknown at present. Coactivators do not appear to bind to specific DNA sequences and it has been suggested that they might act as bridging proteins between activation domains and the TBP. In this sense they would be analogous to the adenovirus E1a protein, which can specifically bind to the ATF activator and can also interact directly with the TBP. Alternatively, they might facilitate direct interactions between activator proteins and the TBP or TFIIB, or other components of the general transcriptional machinery. Another possible mechanism has been suggested by recent studies from R.G. Roeder's group. They have isolated an activity referred to as USA (upstream factor stimulatory activity) which potentiates activation by SP1 and USF in vitro in conjunction with natural TFIID but not the recombinant TBP [54]. USA would therefore appear to have coactivator properties but be less tightly associated with the TBP than the TAFs isolated by Tjian and coworkers. USA was resolved into two components, NC1 (negative cofactor 1) and PC1 (positive cofactor 1) which had opposite effects on core promoter activity: NC1 inhibited, whereas PC1 stimulated basal activity. Interestingly, NC1 could interact directly with the TBP and like TFIIA could stimulate binding of the TBP to the TATA box. TFIIA displaced NC1 from an NC1–TBP complex. Two other activities, NC2 (negative cofactor 2) and DBF4 (TFIID binding factor 4), with similar properties to NC1 have recently been isolated [55]. It has been suggested that these activities might reduce core promoter activity by forming non-productive complexes with TFIID and that activators might reverse this pathway of complex formation (see [6] for a discussion).

5. CONCLUSIONS AND FUTURE PROSPECTS

The hypothesis outlined at the beginning of this article predicts that there should be components of the general transcriptional machinery that are directly contacted by activator proteins. This indeed appears to be

the case. There is now good evidence that VP16, E1a and ZTa specifically interact with the TBP in vitro and that VP16 can interact even more strongly with TFIIB. However, the amino acid residues and protein structures involved in these interactions need to be defined more precisely. This will require detailed mutational analysis of transactivation domains and the regions that they contact in the TBP and TFIIB. The results of such structure/function studies will then need to be related to the 3D-structures of activation domains and their targets as determined by X-ray crystallography or nuclear magnetic resonance.

Another prediction of the hypothesis is that these interactions should lead to an increase in the rate of formation of the transcription initiation complex or in the number of complexes formed. VP16 has been clearly shown to affect the recruitment of TFIIB into preinitiation complex, which was a rate limiting step in the system studied [38] and Zta stabilizes the binding of the TBP to the non-consensus TATA box (GATAAAAG) of the MinL promoter [42]. Analysis of the mechanism of transcriptional activation will be complicated because different activators may function by different mechanisms and a single activator may contact more than one target protein or may behave differently in different promoter contexts. For example, the acidic VP16 activation domain can apparently interact with both the TBP and TFIIB and requires a coactivator activity to be able to stimulate transcription in vitro. This emphasizes the importance of developing simple model systems with well-defined components.

Finally, a novel class of regulatory factors (coactivators) has been identified which appears to play an important role in the process of transcriptional activation. Neither the molecular structure nor mode of action of coactivators is known at present. It will be necessary to purify coactivator polypeptides and obtain the corresponding cDNA clones. It will also be important to obtain genetic evidence to support their existence.

In the budding yeast, *Saccharomyces cerevisiae*, mutations have already been isolated in genes encoding activators, e.g. *GAL4* and *GCN4*, as well in genes for some of the general transcription factors such as the TBP and TFIIB. Interestingly, genetic analysis of several different regulated genes in yeast has identified *trans*-acting loci that are required for the activation of large sets of genes, but which do not encode gene-specific activators or general transcription factors. For example, *SNF2*, *-5* and *-6* are necessary for the efficient transcription of glucose-repressible genes, acid phosphatase, cell type-specific genes and Ty elements, and appear to be functionally interdependent [56]. Similarly, mutations in *SWI1*, *-2* and *-3* not only affect the ability to the *HO* gene to be activated but also a variety of other genes [57]. *SWI2* is in fact identical to *SNF2* and *SWI1* is *ADR6*, a gene required for transcription of *ADH1* and *ADH2*. It has been suggested that *SWI1*, *-2* and *-3* and *SNF5* and *-6* may be components of a large multisubunit complex and that they may function as coactivators [57]. However, since mutations that alter histone H3 or inactivate an HMG 1-like protein alleviate the effects of the swi⁻ mutations (see [57] for refs.) it is equally possible that the role of the *SWI1*, *-2* and *-3* products is to alter chromatin structure so as to make promoters accessible to gene-specific activators. This serves to emphasize the point that whilst direct protein–protein contacts between activators and the general transcription factors will play an important role in transcriptional activation, it is also essential to consider the interactions between activators and chromatin.

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