

Models for Activation of Transcription by Steroid Receptors

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Introduction

A dramatic increase in transcription initiation activity for a given gene can result from the specific binding of steroid-hormone receptor complexes to enhancer sequences (Khoury and Gruss, 1983) called hormone responsive elements (HRE). These receptors act synergistically with other transcription factors to activate transcription by RNA polymerase II from distances of hundreds to thousands of base pairs on either side of the TATA box (Strahl et al, 1988; Schule et al, 1988). Three recent models of activation by hormone receptors—one by Ondek et al. (1988), one by Sigler (1988), and one by Ptashne (1988)—draw on selected properties of the receptors that have been characterized to date. These properties will first be summarized before describing the three models.

Cloning and sequencing of glucocorticoid, progesterone, and estrogen receptors in chicken and human show two highly conserved sequences (Weinberger et al., 1986; Green and Chambon, 1986). One is the binding site for hormone, the binding of which is required for binding of the receptor to the enhancer DNA sequence (Green et al., 1986; Giguere et al., 1986). The other site binds DNA with metal-binding fingers similar to those of TF III for the expression of 5S ribosomal RNA (Freedman et al., 1988).

The DNA HRE enhancer sequences themselves appear as multiple short motifs of 8-10 base pairs. This arrangement has been shown also for thyroxine and simian tumour virus (SV40) (Sap et al., 1986; Ondek et al., 1986). The N-terminal variable region provides the transcription activation function (Tora et al., 1988). Domain swapping experiments using GAL4 in yeast show that the activator domain is functionally interchangeable to a large degree for different genes and across phyla (Hope and Struhl, 1986; Kakidani and Ptashne, 1987). Chimeras in yeast using GAL4 DNA-binding domains and human hormone-binding domains show that induction of activation depends on hormone binding (Webster et al., 1988).

Activator domains are highly acidic with a net negative charge. They do not appear to have a defined structure. Activation is roughly proportional to the fraction of activating region attached. Stronger activating domains can act at greater distances from proximal promoter sites, and multiple bound receptors do not act with a definite stoichiometry (for review see Ptashne, 1988). Recombination of HRE sequences shows that activation is independent of distance or position. HREs consist of binary subunits that are recombinable into chimeras with different activation specificities, and two subunits must be active together for

activation of transcription to occur (Ondek et al., 1988). DNase I sensitivity shows chromatin alteration around active HREs (Zaret and Yamamoto, 1984).

Models

Figure 1 shows Ondek's model where two bound factors, one to each DNA "enhancer" produce one activation domain. Activation is by interaction with proximal promoter factors such as TATA- or CCAAT-binding proteins. Looping of the DNA provides the "action at a distance" mechanism. The adaptive advantage of this arrangement is its role in a larger scheme shown in 1c whereby a greater degree of transcriptional regulation is obtained with a limited number of transcriptional factors.

Figure 2 shows Ptashne's model, which is similar but involves an array of receptors that are "sampled" two at a time by the proximal target transcription factor. Binding of the proximal target protein depends on the number and strength of these interactions.

Sigler's model (Figure 3) is radically different. It is based on the likelihood that the negatively-charged activator polypeptides are conformationally indefinite—hence his term "negative noodles"—plus the suggestion that the carboxy-terminal repeating 7-mer of RNA polymerase II (CT7n) may constitute a long "hitching post" covered with hydroxyl groups. This model goes further to suggest that hydrogen bonding to CT7n, followed by phosphorylation of CT7n, activates transcription, breaks contact with the acidic noodles, and insulates RNA polymerase II from further interaction with negative peptides.

Discussion

Sigler's model is elegant in that it avoids any need for interaction between hormone receptors and other proximal transcription factors, as well as providing a simple explanation for the structure of the RNA polymerase II non-catalytic subunit. On the other hand, this model does not account for the requirement of having two bound receptors for activation.

The Ondek and Ptashne models are more orthodox in that they assume interactions between conformationally fixed structures, which almost seems a forced idea in comparison to Sigler's. Ptashne has done experiments that show that amphiphatic alpha-helices can function in place of the endogenous activator domains, but this does not prove that the activators are fixed structures. However, the Ondek and Ptashne models do allow allosteric conformational changes in response to hormone binding, which may be the mechanism by which hormone binding allows activation to proceed (though neither author addresses this directly). A similar mechanism in Sigler's model seems unlikely.

Determining whether RNA polymerase II is phosphorylated upon activation would perhaps help distinguish whether Sigler's radical model is the more accurate one. Now that the human oestrogen receptor has been shown to activate transcription in a hormone-dependent manner in yeast (Metzger et al, 1988), the answer should be forthcoming.

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