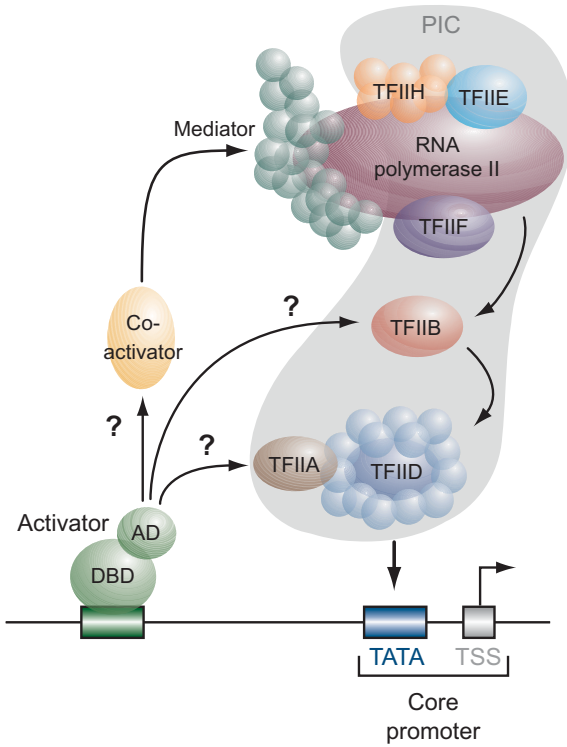

Figure 2

The eukaryotic transcriptional machinery. Factors involved in eukaryotic transcription by RNA polymerase II can be classified into three groups: general transcription factors (GTFs), activators, and coactivators. GTFs, which include RNA polymerase II itself and TFIIA, TFIIB, TFIID, TFIIE, TFIIF, and TFIIH, assemble on the core promoter in an ordered fashion to form a preinitiation complex (PIC), which directs RNA polymerase II to the transcription start site (TSS). Transcriptional activity is greatly stimulated by activators, which bind to upstream regulatory elements and work, at least in part, by stimulating PIC formation through a mechanism thought to involve direct interactions with one or more components of the transcriptional machinery. Activators consist of a DNA-binding domain (DBD) and a separable activation domain (AD) that is required for the activator to stimulate transcription. The direct targets of activators are largely unknown.

extensive discussion of the properties of activators is beyond the scope of this review; readers are referred to several excellent reviews on the subject (87 and references therein).

The DNA-binding sites for activators [also called transcription factor-binding sites (TFBSs)] are generally small, in the range of 6–12 bp, although binding specificity is usually dictated by no more than 4–6 positions within the site. The TFBSs for a specific activator are typically degenerate, and are therefore described by a consensus sequence in which certain positions are relatively constrained and others are more variable. Many activators form heterodimers and/or homodimers, and thus their binding sites are generally composed of two half-sites. Notably, the precise subunit composition of an activator can also dictate its binding specificity and regulatory action (37).

Although an activator can bind to a wide variety of sequence variants that conform to the consensus, in certain instances the precise sequence of a TFBS can impact the regulatory output. For example, TFBS sequence variations can affect activator binding strength (reviewed in 30), which may be biologically important in situations such as in early development, in which activators are distributed in a concentration gradient (84, 144). TFBS sequence variations may also direct a preference for certain dimerization partners over others (37, 124, 142). Finally, the particular sequence of a TFBS can affect the structure of a bound activator in a way that alters its activity (69, 104, 108, 154, 163). The best-studied examples are nuclear hormone receptors, a large class of ligand-dependent activators. Various studies have shown that the relative orientation of the half-sites, as well as the spacing between them, play a major role in directing the regulatory action of the bound nuclear hormone receptor dimer (37).

Activators work, at least in part, by increasing PIC formation through a mechanism thought to involve direct interactions with one or more components of the transcriptional machinery, termed the "target" (141, 149). Activators may also act by promoting a step in the transcription process subsequent to PIC assembly, such as initiation, elongation, or reinitiation (103). Finally, activators have also been proposed to function by recruiting activities that modify chromatin structure (47, 106). Chromatin often poses a barrier to transcription because it prevents the transcriptional machinery from interacting directly with promoter DNA, and thus can be

TBP: TATA-box-binding protein

TAF: TBP-associated factor

TFBS: transcription factor-binding site