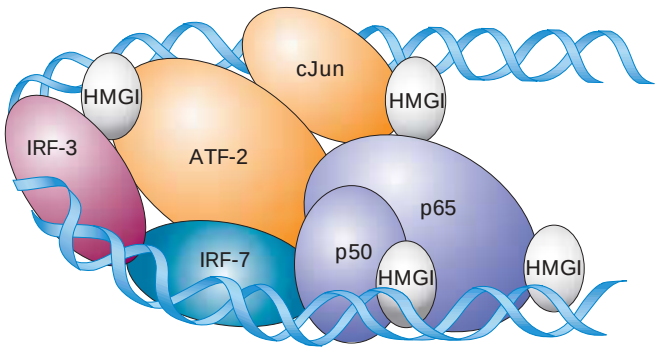
genetic studies indicate that repression domains also mediate protein-protein interactions and bind to *co-repressor* proteins, forming a complex that inhibits transcription initiation by mechanisms that are discussed later in the chapter.

Multiprotein Complexes Form on Enhancers

As noted previously, enhancers generally range in length from about 50 to 200 base pairs and include binding sites for several transcription factors. The multiple transcription factors that bind to a single enhancer are thought to interact. Analysis of the ≈70-bp enhancer that regulates expression of **β-interferon,** an important protein in defense against viral infections in humans, provides a good example of such transcription-factor interactions. The β-interferon enhancer contains four control elements that bind four different transcription factors simultaneously. In the presence of a small, abundant protein associated with chromatin called *HMGI,* binding of the transcription factors is highly cooperative, similar to the binding of NFAT and AP1 to the composite promoter-proximal site in the *IL-2* control region (see Figure 11-24). This cooperative binding produces a multiprotein complex on the β-interferon enhancer DNA (Figure 11-26). The term **enhancesome** has been coined to describe such large nucleoprotein complexes that assemble from transcription factors as they bind cooperatively to their multiple binding sites in an enhancer.

HMGI binds to the minor groove of DNA regardless of the sequence and, as a result, bends the DNA molecule sharply. This bending of the enhancer DNA permits bound transcription factors to interact properly. The inherently weak, noncovalent protein-protein interactions between transcription factors are strengthened by their binding to neighboring DNA sites, which keeps the proteins at very high relative concentrations.

Because of the presence of flexible regions connecting the DNA-binding domains and activation or repression domains in transcription factors (see Figure 11-18) and the ability of bound proteins to bend DNA, considerable leeway in the spacing between regulatory elements in transcription-control regions is permissible. This property probably contributed to rapid evolution of gene control in eukaryotes. Transposition of DNA sequences and recombination between repeated sequences over evolutionary time likely created new combinations of control elements that were subjected to natural selection and retained if they proved beneficial. The latitude in spacing between regulatory elements probably allowed many more functional combinations to be subjected to this evolutionary experimentation than would be the case if constraints on the spacing between regulatory elements were strict.



▲ FIGURE 11-26 **Model of the enhancesome that forms on the β-interferon enhancer.** Two monomeric transcription factors, IRF-3 and IRF-7, and two heterodimeric factors, Jun/ATF-2 and p50/ p65 (NF-κB) bind to the four control elements in this enhancer. Cooperative binding of these transcription factors is facilitated by HMGI, which binds to the minor groove of DNA and also interacts directly with the dimeric factors. Bending of the enhancer sequence resulting from HMGI binding is critical to formation of an enhancesome. Different DNA-bending proteins act similarly at other enhancers. [Adapted from D. Thanos and T. Maniatis, 1995, *Cell* **83**:1091, and M. A. Wathel et al., 1998, *Mol. Cell* **1**:507.]

KEY CONCEPTS OF SECTION 11.3

Activators and Repressors of Transcription

- Transcription factors, which stimulate or repress transcription, bind to promoter-proximal regulatory elements and enhancers in eukaryotic DNA.
- Transcription activators and repressors are generally modular proteins containing a single DNA-binding domain and one or a few activation domains (for activators) or repression domains (for repressors). The different domains frequently are linked through flexible polypeptide regions (see Figure 11-18).
- Among the most common structural motifs found in the DNA-binding domains of eukaryotic transcription factors are the C_2H_2 zinc finger, homeodomain, basic helix-loop-helix (bHLH), and basic zipper (leucine zipper). All these and many other DNA-binding motifs contain one or more α helices that interact with major grooves in their cognate site in DNA.
- The transcription-control regions of most genes contain binding sites for multiple transcription factors. Transcription of such genes varies depending on the particular repertoire of transcription factors that are expressed and activated in a particular cell at a particular time.
- Combinatorial complexity in transcription control results from alternative combinations of monomers that form heterodimeric transcription factors (see Figure 11-23) and from cooperative binding of transcription factors to composite control sites (see Figure 11-24).
- Activation and repression domains in transcription factors exhibit a variety of amino acid sequences and three-dimensional structures. In general, these functional do-