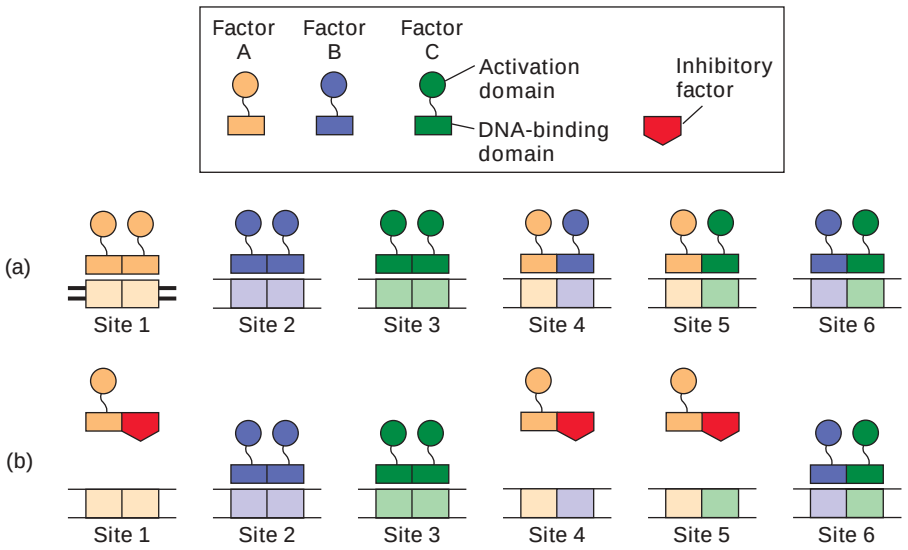
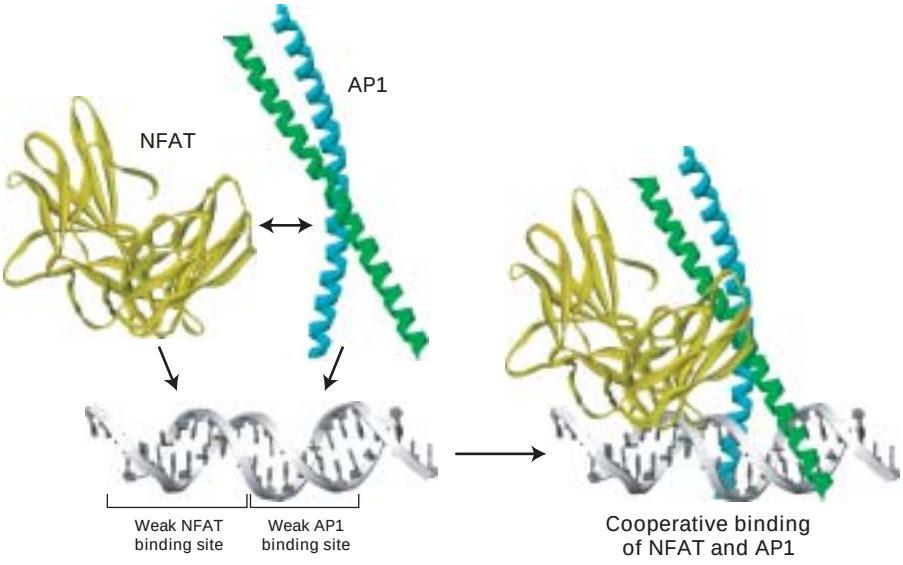


▶ FIGURE 11-23 **Combinatorial possibilities due to formation of heterodimeric transcription factors.** (a) In the hypothetical example shown, transcription factors A, B, and C can all interact with one another, permitting the three factors to bind to six different DNA sequences (sites 1–6) and creating six combinations of activation domains. Each composite binding site is divided into two half-sites, and each heterodimeric factor contains the activation domains of its two constituent monomers. (b) Expression of an inhibitory factor (green) that interacts only with factor A inhibits binding; hence, transcriptional activation at sites 1, 4, and 5 is inhibited, but activation at sites 2, 3, and 6 is unaffected.

transcription factors bound to closely spaced binding sites in DNA. An example is the interaction of two transcription factors, NFAT and AP1, which bind to neighboring sites in a composite promoter-proximal element regulating the gene encoding interleukon-2 (IL-2). Expression of the *IL-2* gene is critical to the immune response, but abnormal expression of IL-2 can lead to autoimmune diseases such as rheumatoid arthritis. Neither NFAT nor AP1 binds to its site in the *IL-2* control region in the absence of the other. The affinities of the factors for these particular DNA sequences are too low for the individual factors to form a stable complex with DNA. However, when both NFAT and AP1 are present, protein-protein interactions between them stabilize the DNA ternary complex composed of NFAT, AP1, and DNA (Figure 11-24). Such *cooperative DNA binding* of various transcription factors results in considerable combinatorial complexity of transcription control. As a result, the approximately 2000 transcription factors encoded in the human genome can bind to DNA through a much larger number of cooperative interactions, resulting in unique transcriptional control for each of the several tens of thousands of human genes. In the case of *IL-2*, transcription occurs only when both NFAT is activated, resulting in its transport from cytoplasm to the nucleus, and the two subunits of AP1 are synthesized. These events are controlled by distinct signal transduction pathways (Chapters 13 and 14), allowing stringent control of IL-2 expression.

Cooperative binding by NFAT and AP1 occurs only when their weak binding sites are located at a precise distance, quite close to each other in DNA. Recent studies have shown that the requirements for cooperative binding are not so stringent in the case of some other transcription factors and control regions. For example, the *EGR-1* control region contains a composite binding site to which the SRF and TCF



▶ FIGURE 11-24 **Cooperative binding of two unrelated transcription factors to neighboring sites in a composite control element.** By themselves, both monomeric NFAT and heterodimeric AP1 transcription factors have low affinity for their respective binding sites in the *IL-2* promoter-proximal region. Protein-protein interactions between NFAT and AP1 add to the overall stability of the NFAT-AP1-DNA complex, so that the two proteins bind to the composite site cooperatively. [See L. Chen et al., 1998, *Nature* **392**:42.]