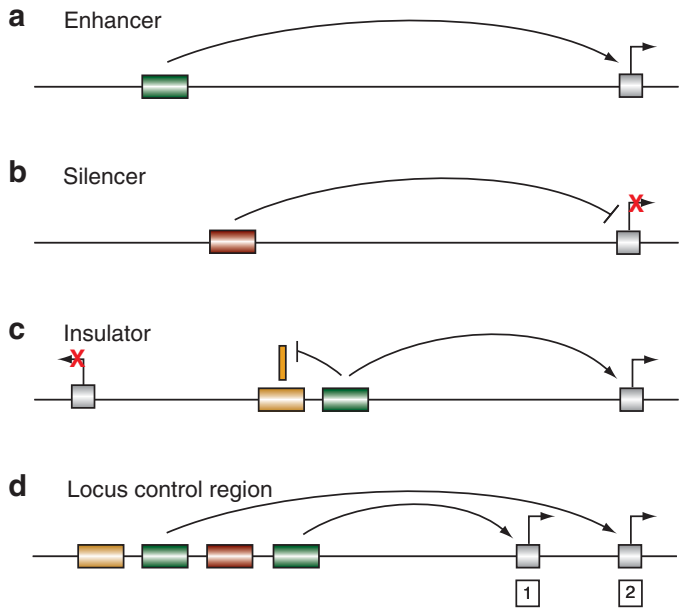

Figure 4

Distal transcriptional regulatory elements. (*a*, *b*) Enhancers and silencers function to activate and repress transcription, respectively. (*c*) Insulators function to block genes from being affected by the transcriptional regulatory elements of neighboring genes. (*d*) Locus control regions are typically composed of multiple regulatory elements that function together to confer proper temporal- and/or spatial-specific gene expression to a cluster of nearby genes.

different times or in different tissues, or in response to different stimuli (reviewed in 7). Enhancers are typically composed of a relatively closely grouped cluster of TFBSs that work cooperatively to enhance transcription. The spatial organization and orientation of TFBSs within an enhancer can be critical to its regulatory activity (154, 178); thus, the properties of distance- and orientation independence only apply to the enhancer cluster as a whole.

Enhancers are functionally similar to proximal promoter elements, and the distinction between the two classes is somewhat blurred. In fact, in many cases, the same activators that bind enhancer elements also bind proximal promoter elements in different genes. However, unlike most proximal promoter elements, enhancers are typically long-distance transcriptional control elements that can be situated quite distally from the core promoter (**Figure 4*a***). For example, enhancers can reside several hundred kilobase pairs upstream of a promoter, downstream of a promoter in an intron, or even beyond the 3′ end of the gene (107 and reviewed in 20).

How do distal elements function over such long physical distances? Data are accumulating in favor of a DNA-looping model, whereby the enhancer and core promoter are brought into close proximity by "looping out" the intervening DNA. A number of recent studies suggest that the DNA-looping model may in fact be a general mechanism by which enhancers function (reviewed in 184). Interestingly, studies have also suggested that PIC formation may begin at a distal enhancer (175), not at the core promoter, as is usually assumed. This would allow for more precise control of the timing of transcription activation, and may be more common in cases in which rapid gene activation is required.

Silencers

Silencers are sequence-specific elements that confer a negative (i.e., silencing or repressing) effect on the transcription of a target gene (**Figure 4*b***). They generally share most of the properties ascribed to enhancers (reviewed in 140). Typically, they function independently of orientation and distance from the promoter, although some position-dependent silencers have been encountered. They can be situated as as part of a proximal promoter, as part of a distal enhancer, or as an independent distal regulatory module; in this regard, silencers can be located far from their target gene, in its intron, or in its 3′-untranslated region. Finally, silencers may cooperate in binding to DNA (74), and they can act synergistically (164).

Silencers are binding sites for negative transcription factors called repressors. Repressor function can require the recruitment of negative cofactors, also called corepressors (148), and in some cases, an activator can switch to a repressor by differential cofactor