

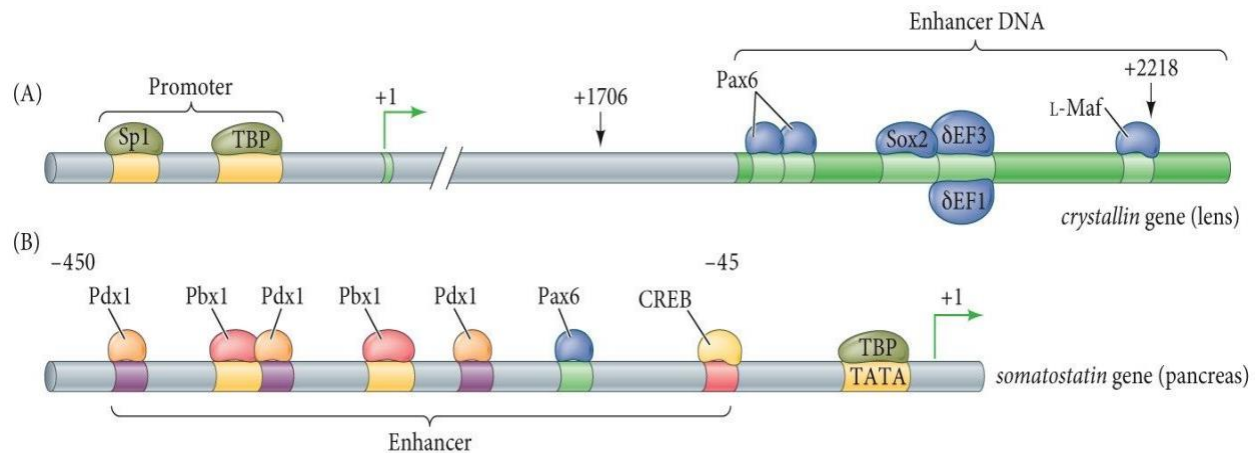
Combinatorial Association

Although there is modularity *among* enhancers, there are codependent units *within* each enhancer. Enhancers contain regions of DNA that bind transcription factors, and it is this *combination* of transcription factors that activates the gene. For instance, the pancreas-specific enhancer of the *Pax6* gene has binding sites for the Pbx1 and Meis transcription factors (see Figure 3.8C in the text). Both need to be present for the enhancer to activate *Pax6* in the pancreas cells (Zhang et al. 2006).

Moreover, the product of the *Pax6* gene encodes a transcription factor that works in combinatorial partnerships with other transcription factors. Figure FDO 3.2 shows two gene enhancer regions that bind *Pax6*. The first is that of the chick $\delta 1$ lens *crystallin* gene (Figure 1A; Cvekl and Piatigorsky 1996; Muta et al. 2002). This gene encodes crystallin, a lens protein that is transparent and allows light to reach the retina. A promoter in the *crystallin* gene contains binding sites for TBP and Sp1 (basal transcriptional factors that recruit RNA polymerase II to the DNA). The gene also has an enhancer in its third intron that controls the time and place of crystallin expression. This enhancer has two Pax6-binding sites. The Pax6 protein works with the Sox2 and L-Maf transcription factors to activate the *crystallin* gene only in those head cells that are going to become lens. As we will see in Chapter 16, this means that the cell (1) must be head ectoderm (which expresses Pax6), (2) must be in the region of the ectoderm capable of forming eyes (expressing L-Maf), and (3) must be in contact with the future retinal cells (which induce Sox2 expression; see Kamachi et al. 1998).

Meanwhile, Pax6 also regulates the transcription of the genes encoding insulin, glucagon, and somatostatin in the pancreas (Figure 1B). Here, Pax6 works in cooperation with other transcription factors such as Pdx1 (specific for the pancreatic region of the endoderm) and Pbx1 (Andersen et al. 1999; Hussain and Habener 1999). So in the absence of Pax6, the eye fails to form, and the endocrine cells of the pancreas do not develop properly; these improperly developed endocrine cells produce deficient amounts of their hormones (Sander et al. 1997; Zhang et al. 2002).

Other genes are activated by Pax6 binding, and one of them is the *Pax6* gene itself. Pax6 protein can bind to a *cis*-regulatory element of the *Pax6* gene (Plaza et al. 1993). So once the *Pax6* gene is turned on, it will continue to be expressed, even if the signal that originally activated it is no longer present.



A after Cvekl and Piatigorsky 1996; B after Andersen et al. 1999

Figure 1 Modular transcriptional regulatory regions using Pax6 as an activator. (A) Promoter and enhancer of the chick $\delta 1$ lens *crystallin* gene. Pax6 interacts with two other transcription factors, Sox2 and L-Maf, to activate this gene. The protein δ EF3 binds factors that permit this interaction; δ EF1 binds factors that inhibit it. (B) Promoter and enhancer of the rat *somatostatin* gene. Pax6 activates this gene by cooperating with the Pbx1 and Pdx1 transcription factors. (A after Cvekl and Piatigorsky 1996; B after Andersen et al. 1999.)

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