EXPLORE THE ISSUE BEING INVESTIGATED

How Regulatory Genes Direct Vertebrate Development

The hallmark of vertebrate development is that it is a gene-regulated process. Unlike plants, in which the progression of development is keyed to environmental signals, animals employ a carefully-timed array of gene signals to direct development. The investigation of how vertebrate regulatory genes direct development has been, and continues to be, one of the most exciting research areas in biology.

In order to sort out this very complicated business, it is necessary to focus on specific systems. If you can understand one system in detail, what you learn may apply to other systems as well, and eventually, when many systems have been investigated, a general picture emerges.

The anterior pituitary gland presents a valuable model system for studying vertebrate development. The mature gland contains five discrete cell types, each of which secretes one or more specific polypeptide hormones. One type secretes GH (growth hormone), another secretes TSH (thyroid-stimulating hormone), a third secretes PRL (prolactin), a fourth secretes LH (luteinizing hormone) and FSH (follicle-stimulating hormone), and a fifth secretes ACTH (adrenocorticotropin hormone).

Early in development, an inductive signal kicks off the formation of the pituitary gland. How does the embryo control the production of these five cell types as the gland is formed, so that all five cell types are formed in the right place, at the right time?

The control is carried out by an array of special transcription factors. Transcription factors are regulatory proteins that facilitate the transcription of particular genes. Without the appropriate transcription factors to guide and stabilize it, RNA polymerase cannot properly attach to and read the gene. Thus to control when the gene is expressed, the embryo controls availability of the required transcription factors.

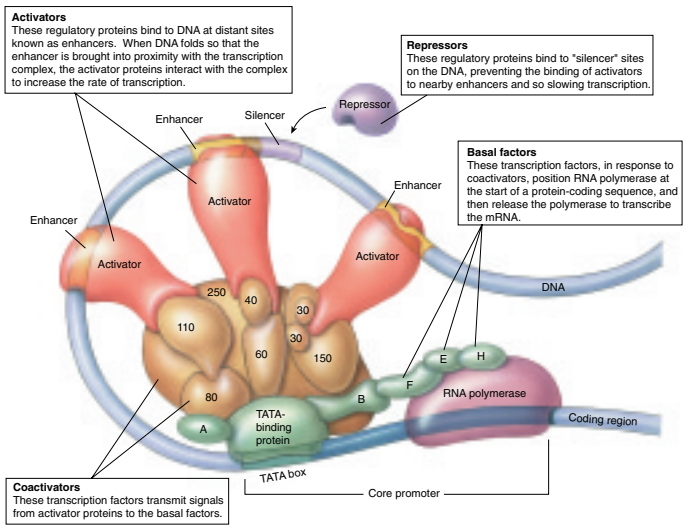
A transcription factor is composed of discrete regions, called domains, each of which has a different job to do (see figure *above*). To understand how the domains of a transcription factor work together to influence a particular gene's transcription, let's focus on one of the transcription factors controlling pituitary development. Called LHX3, this protein is produced in two isoforms (LHX3a and LHX3b) that appear to have different functions in the cell but both contain two kinds of domains to perform the following functions:

1. *Binding the transcription factor to its target gene.* One of LHX3's domains is a DNA-binding domain that directs the transcription factor to bind to the appropriate gene locations governing determination and differentiation of the five cell types.

2. *Regulating the target gene.* Two of LHX3's domains mediate protein-protein interactions once the transcription factor has attached to the DNA. By having particular shapes that bump into the regulatory proteins Pit-1 and NLI in just such a way, these domains influence what happens as the polymerase attempts to transcribe the genes directing production of the cell types.

In humans, two mutations in the *LHX3* gene have recently been described. Both block production of all pituitary hormones, leading to a growth-retarding gene disorder known as "combined pituitary hormone deficiency." One mutation changes a single amino acid in one of the protein-protein interaction domains (a tyrosine to a cysteine), while the other clips off the DNA-binding domain.

In order to gain a clearer idea of how the transcription factor LHX3 mediates proper development of pituitary cell types, the laboratory of Simon Rhodes at Indiana University-Purdue University has investigated the molecular basis of the two *LHX3* defects. Their basic strategy is to compare the gene regulatory properties of normal and mutant forms of the LHX3 transcription factor. Any differences that are seen may provide clues about how the transcription factor functions in human development.



A transcription factor. This protein complex brings DNA and RNA polymerase into proper orientation for transcription to occur.