Development of the Cerebral Cortex: IV. Transcription Factors

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One hundred thousand genes are estimated to lie on the full complement of human chromosomes. Of these, fully one third are thought to be specifically expressed within the central nervous system. The proteins encoded by these approximately 30,000 genes are expressed at different developmental periods. Many exert their effects during early brain development, while others are expressed only in more mature neurons when specific neurotransmitters or their receptors are required. Finally, another set of genes encode structural and essential cellular proteins, and these genes are expressed continuously during the life of the neuron. It is important to appreciate how this genetic blueprint unfolds, as disturbances of this process affect the development of the central nervous system. Recently, the mutations for several developmental disorders were found to be in the genes for a family of regulatory proteins that are called transcription factors. In this column, the role of transcription factors in regulating gene expression within the developing brain will be reviewed.

The basic flow of biological information within any cell is from DNA to RNA to protein. Gene expression can be regulated at a number of steps in this pathway. The first level of control occurs by regulating how often and at what developmental periods a particular gene is transcribed into RNA. This form of regulation is termed transcriptional control. However, additional levels of control also exist. For example, after the initial transcription of RNA from DNA, the resultant RNA molecule must be processed into a more mature RNA transcript. These mature messages are then transported from the nucleus, where they are synthesized, into the cytoplasm, where they are translated into proteins required by that cell. Regulating the amount of message produced, as well as its life span, affects the amount of protein that is eventually present. Moreover, once proteins are synthesized, they are often modified by additional mechanisms, such as phosphorylation and glycosylation. Control mechanisms have evolved for each of these steps, and their disruption leads to a number of neuropsychiatric disorders, including Waardenburg syndrome, Prader-Willi syndrome, and fragile X syndrome.

Transcriptional control of genes is found throughout the animal kingdom. The mechanism lies within the promoter region of a gene, a region that is usually found immediately adjacent to the site at which transcription is initiated. Two fundamental components are required (Fig. 1). The first is the presence of short stretches of DNA within the promoter region. The second component consists of regulatory proteins that recognize these stretches of DNA and bind tightly to them. These proteins are termed transcription factors, and the binding of one or more transcription factors within a promoter region determines whether transcription of that

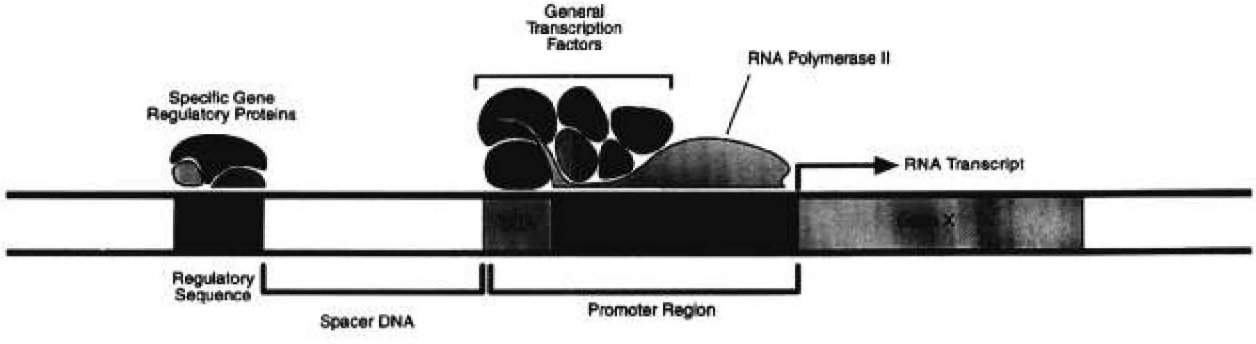

Fig. 1 The regulation of transcription from DNA into RNA transcripts is a tightly controlled process. Transcription factors bind to DNA sequences within a regulatory region termed the promoter and determine the amount of transcription that occurs from the gene in question. In the figure, one of the nucleotide sequences is shown *(TATA box)*. A number of transcription factors bind to this site and to each other. Only then is the transcription enzyme RNA polymerase allowed access to the DNA and is transcription initiated. Regulatory sequences are also found further upstream and serve to bind additional transcription proteins. Each gene varies in both the number and type of regulatory sequences that are present, adding a further level of control over exactly which genes are activated in any given tissue. From Alberts et al. (1994), *Molecular Biology of the Cell*, 3rd ed. New York: Garland Publishing, p. 424 (adapted with permission).

gene can proceed. Other regulatory sequences often lie further upstream, and the binding of additional proteins to these sequences provides for fine-tuning of the level of transcription from the gene. The combined actions of these transcription factors may enhance or suppress the transcription of the gene in question.

It is clear from this discussion that a complex interplay of regulatory proteins occurs within the brain to determine whether and how much of a particular protein is expressed. Transcription factors are themselves regulated by signals that arrive at the surface of a cell. For example, the transcription factor CREB is activated in many cells in response to a neurotransmitter that initiates a cascade of signals within the neurons that receive them. The arrival of a signal at the surface of a cell often leads to the rapid activation of transcription factors that are transported to the nucleus and initiate the transcription of specific target genes.

One of these signals leads to the production of the second messenger, cyclic AMP. Second messengers participate in the transmission of signals from the surface of a cell to its interior. Thus, after a neurotransmitter binds to its receptor, cyclic AMP is produced immediately inside the cell. Cyclic AMP initiates an enzymatic pathway that activates the transcription factor, CREB. Activated CREB molecules are rapidly transported to the nucleus, where they recognize and bind to specific nucleotide sequences in the promoter region of a number of genes. In this way, CREB initiates the transcription and eventual synthesis of proteins required by the cell at that particular moment.

As CREB is highly expressed in cells throughout the body, mutations within this important regulatory protein, or an associated protein that is required for CREB activity, might be expected to affect a number of different organ systems. This is in fact the case. A mutation within a gene that encodes a CREB-associated protein was recently found to be responsible for Rubinstein-Taybi syndrome, a rare autosomal recessive disorder that affects approximately 1 per 300 institutionalized individuals with mental retardation. The clinical symptoms of this syndrome include not only mental retardation and agenesis of the corpus callosum, but additional malformations throughout the body including the heart, skin, and skeletal systems. The multitude of congenital problems makes sense once one appreciates the role of CREB as a transcription factor. CREB is required to turn on the expression of many additional proteins that are necessary for the normal growth and development of cells throughout the body, and its absence leads to the multiple congenital abnormalities.

WEB SITES OF INTEREST

http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?180849
http://sdb.bio.purdue.edu/fly/aimain/wtnw13a.htm

ADDITIONAL READINGS

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