Development of the Cerebral Cortex: V. Transcription Factors and Brain Development

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As was discussed in the last Development and Neurobiology column (see the April issue of the *Journal*), transcription factors regulate the expression of proteins that are necessary during the development of specific tissues throughout the body. This is true in the brain as well. Over the past decade, transcription factors that are expressed in regionally restricted patterns within the developing brain have been identified. Often their patterns of expression respect boundaries that delimit major brain subdivisions. For instance, some transcription factor genes are expressed in the developing cerebral cortex (*Emx-1* and *-2*), whereas others are found in the developing basal ganglia (*Dlx-1* and *-2*) (Fig. 1).

Many types of transcription factors are expressed in the brain. Classes of transcription factors are defined on the basis of the amino acid sequences of their DNA binding motifs, which include the homeodomain, helix-loop-helix, and T box. Relatively little is known about the genes that are regulated by transcription factors. However, through analyses of mice with mutations in these genes, termed "knock-out" mice, we are beginning to understand their roles in controlling the development of particular regions of the brain.

In an effort to determine the function of unknown genes and their protein products, investigators are now able to generate mice that lack the expression of a particular gene. They raise the mice in the laboratory and study the effects that lacking this gene might have on the growth, development, and survival of the animal. A number of such knock-out mouse models have been generated, and some of these will be reviewed in this column as they have been shown to have interesting phenotypes, particularly in the area of hyperactivity and aggression. Similar efforts have been

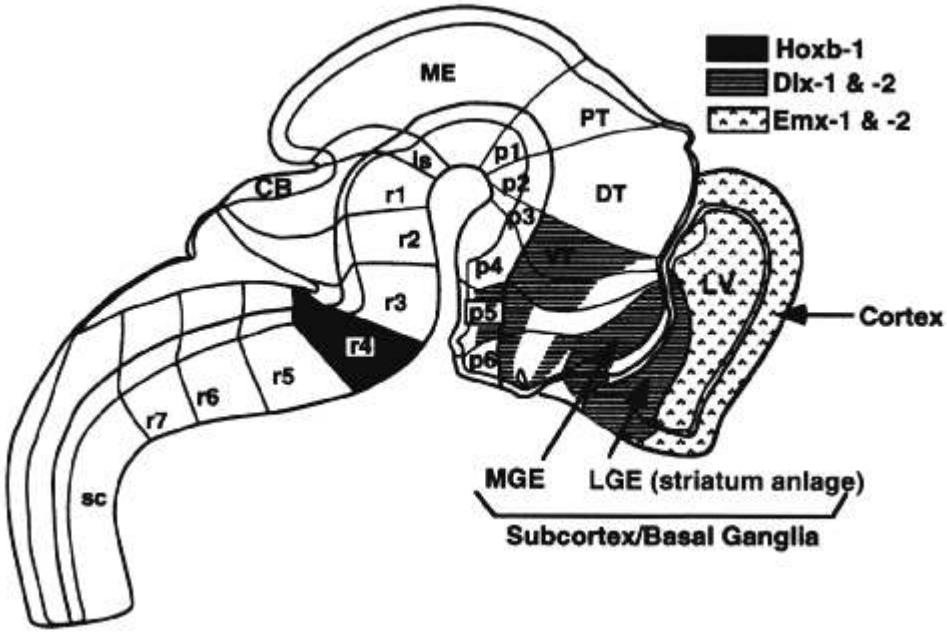

Fig. 1 Schematic diagram of embryonic brain organization showing the principal expression domains of *Hoxb-1*, *Dlx-1*, *Dlx-2*, *Emx-1*, and *Emx-2* in the hindbrain, ventral thalamus and basal ganglia, and cerebral cortex, respectively. The expression domains respect boundaries that delineate the transverse and longitudinal subdivisions of the central nervous system. CB = cerebellum; DT = dorsal thalamus; is = isthmus; LGE = lateral ganglionic eminence; LV = lateral ventricle; MGE = medial ganglionic eminence; ME = mesencephalon; p1–6 = prosomeric subdivisions; PT = pretectum; r1–7 = rhombomeric subdivisions; sc = spinal cord; VT = ventral thalamus.

applied to homeobox genes to determine the contribution these genes make to the development of the brain.

Different classes of homeobox genes tend to be expressed in different regions of the brain and are critical to the development of that specific region. Thus, mutations of the *Hox* genes disrupt the hindbrain and cause loss of many of the cranial nerves. Mutations in the *Engrailed* genes disrupt the development of the cerebellum and midbrain. Finally, mutations of the *Dlx* genes affect differentiation in the basal ganglia, while mutations of the *Emx* and *Otx* genes affect the cerebral cortex.

Several generalizations can be made from these studies. The defects in the mutant animals are frequently subtle. This is because there are often several highly related transcription factors in the same tissue, and the closely related gene products are able to take over the function of the mutated gene. Thus, to determine further the effects of these genes on development, investigators are now creating "double knockouts" in which both genes are removed. When animals have mutations in two of these related genes, they often have much more severe abnormalities. For instance, mutation of *Dlx-2* affects one type of interneuron in the olfactory bulb, whereas mutation of both *Dlx-1* and *Dlx-2* appears to affect all of the interneurons in this region.

Homeobox genes regulate processes ranging from the specification of the identity of brain regions to the growth of these regions to participating in the differentiation of specific cell types or axon tracts. Mutation of *Emx-2* eliminates the dentate gyrus of the hippocampus, and mutation of *Emx-1* primarily reduces the corpus callosum. In addition, in humans, mutations of *Emx-2* result in a type of cerebral cortical malformation called schizencephaly. Thus, these genes are essential for major aspects of brain development, and their absence or mutation causes abnormalities in specific cell types or in the "wiring" within the brain. Mutations or subtle variations in the activity level of some of these master control protein deficits are hypothesized to be associated with the more commonly seen neuropsychiatric disorders.

WEB SITES OF INTEREST

http://www.biozentrum.unibas.ch/~zellbio/gehring.html
http://flybase.bio.indiana.edu:82/allied-data/lk/interactive-fly/aimain/1aahome.htm

ADDITIONAL READINGS

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