Development of the Cerebral Cortex: I. Forming the Cortical Structure

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Laboratories around the world are exploring the intricacies of how the human central nervous system develops. Understanding the mechanisms of cortical development gives essential insight into the pathogenesis of many genetic and acquired developmental psychiatric disorders, including autism, schizophrenia, and learning disabilities. Over the next several months, this column will highlight aspects of normal and abnormal cortical development. We will report on recently isolated molecules that have been discovered to participate in brain growth and development. We will discuss the functions of these proteins and how mutations in them disrupt the normal developmental trajectory of the children we see in our offices.

Neurons of the cerebral cortex form a highly organized laminar and radial structure. The adult human cortex is characterized by six layers, each consisting of specialized neurons with specific phenotypes and synaptic connections (Fig. 1A). Although in most organs, cells are born near their eventual location, in the embryonic development of the cortex, neurons are generated some distance away. The final migration of these neurons and the establishment of proper interneuronal connections are critical for proper cortical functioning. Defects in this dynamic process underlie a number of developmental disorders of higher brain function.

The first neurons destined to settle in the human cortex are produced during the first half of gestation, deep within the brain and close to the cavity of the cerebral ventricle in a region called the ventricular zone. Shortly after their last mitotic divisions, these neurons migrate outward toward the pial surface of the cortex, where they form a sheet of cells called the cortical plate. Each successive generation of migrating neurons passes through the previously born cells before arriving at the final destination at the interface between the cortical plate and the marginal zone (Fig. 1B). During migration, neurons use a transient population of radial glial cells (Fig. 1C) as a scaffolding to aid their nav-

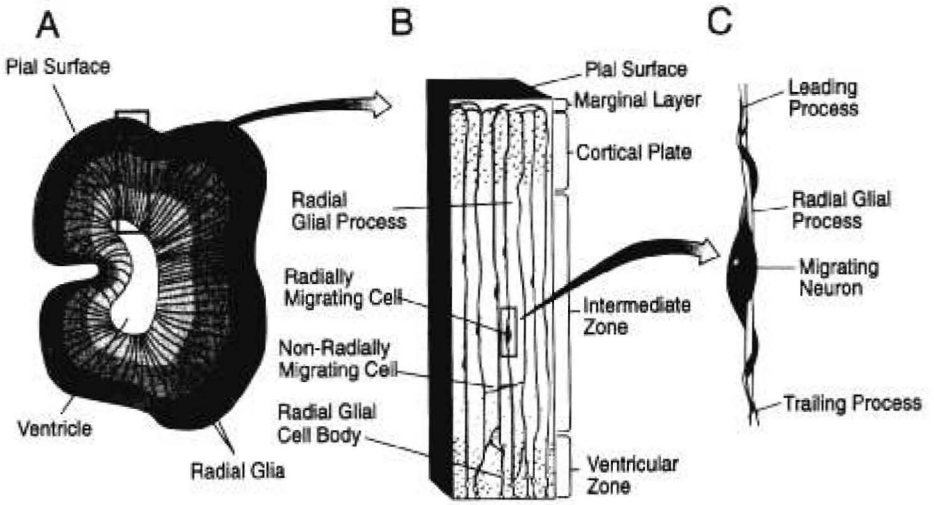

Fig. 1 Normal development of the cerebral cortex. (*A*) Section through the developing primate forebrain showing distribution pattern of radial glial processes that span fetal cerebral wall from the ventricle to the pial surface. (*B*) Enlargement of the boxed area in (*A*) to illustrate how neurons migrate from their birth place in the ventricular zone across the intermediate zone to their final destination at the interface between the marginal zone and the developing cortical plate. (*C*) Neuroblasts use the surface of elongated radial glial fibers as a guide during their migration. From Rakic P (1972), Mode of cell migration to the superficial layers of fetal monkey neocortex. *J Comp Neurol* 145:61–83, copyright © 1972, John Wiley & Sons.

igation. These cells form long fascicles that span the cerebral cortex and guide the migrating neurons through each cortical layer. According to the radial unit hypothesis of cortical development, the horizontal location of cortical neuron is determined by the position of its precursor cells in the proliferative ventricular zone, while its depth results from its birth order.

This pattern of development has two major consequences. First, the cortex develops in an inside-out pattern in which the earliest-born neurons are found in the deepest cortical layers and the later-born neurons move to the more superficial layers. Second, the radial glial hypothesis provides an explanation for the columnar organization of the cortex. Each group of progenitor cells within the ventricular zone gives rise to a column of interrelated neurons above it. After the neurons have taken their proper laminar positions, they develop characteristic synaptic connections with nearby neurons as well as more distant neurons in associated regions of the cortex.

Disruptions of neuronal migration have been found in several developmental disorders, such as lissencephaly and movement disorders (such as the *reeler* mutation in mice). The molecular basis for these disorders will be discussed in the next two columns. In addition, more subtle disruptions of migration and in the development of synaptic connections have been proposed for more common disorders such as dyslexia and psychosis.

WEB SITE OF INTEREST

http://info.med.yale.edu/neurobio/rakic/rakic.html (visit this site on the Internet depicting animated version of cellular events during early cortical development)

ADDITIONAL READINGS

Hatten M (1993), The role of migration in central nervous system neuronal development. *Curr Opin Neurobiol* 3:38–44

Levitt P, Barbe M, Eagleson K (1997), Patterning and specification of the cerebral cortex. *Annu Rev Neurosci* 20:1–24

Mountcastle V (1997), The columnar organization of the neocortex. *Brain* 120:701–722

Rakic P (1988), Specification of cerebral cortical areas. *Science* 241:170–176

Rakic P (1995), Radial versus tangential migration of neuronal clones in the developing cerebral cortex. *Proc Natl Acad Sci* 92:11323–11327

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