Development of the Cerebral Cortex: III. The *Reeler* Mutation

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Mutant mouse strains provide insight into the underlying molecular mechanisms of the development of the CNS. These spontaneous mutations were first identified by scientists interested in motor behavior, and it proved relatively easy to screen litter mates for mice that showed difficulties moving around the cage. A number of such mice were found and given descriptive names such as *reeler*, *weaver*, *lurcher*, *nervous*, and *staggerer*.

On microscopic study of the brains of these mice, researchers found evidence of abnormal neuronal migration within the cerebellar and cerebral cortices, as well as degeneration of classes of neurons. It was not until the advent of recombinant DNA techniques, however, that the genes responsible for the observed CNS abnormalities could actually be isolated.

The gene for one of these mutant strains, *reeler*, was recently cloned. The *reeler* mutation causes an abnormal laminar pattern to develop in the cerebral and cerebellar cortices. As was discussed in the last two Development and Neurobiology columns (see January and February issues of the *Journal*), the normal migration of neurons in the cerebral cortex follows an "inside-out" pattern, in which later-generated neurons pass by the earlier-born neurons in their migration to their final destination. In the *reeler* mouse, this normal migratory path is reversed (Fig. 1). The earliest-born neurons migrate to the surface, the next generation of neurons settles immediately below, and the final neurons form the deepest cortical layer.

The *reeler* gene makes a protein called reelin. In the normally developing brain, reelin is expressed at its highest levels during the period when neurons are born and beginning their migration. Reelin is not found in all cells of the cerebral cortex but is produced within a unique family of cells located at the cortical surface (Cajal-Retzius cells in Fig. 1). The amino acid structure of reelin is very similar to that of proteins known to be secreted into the extracellular matrix surrounding neurons. These proteins are believed to help guide neurons as they migrate through the central and peri-

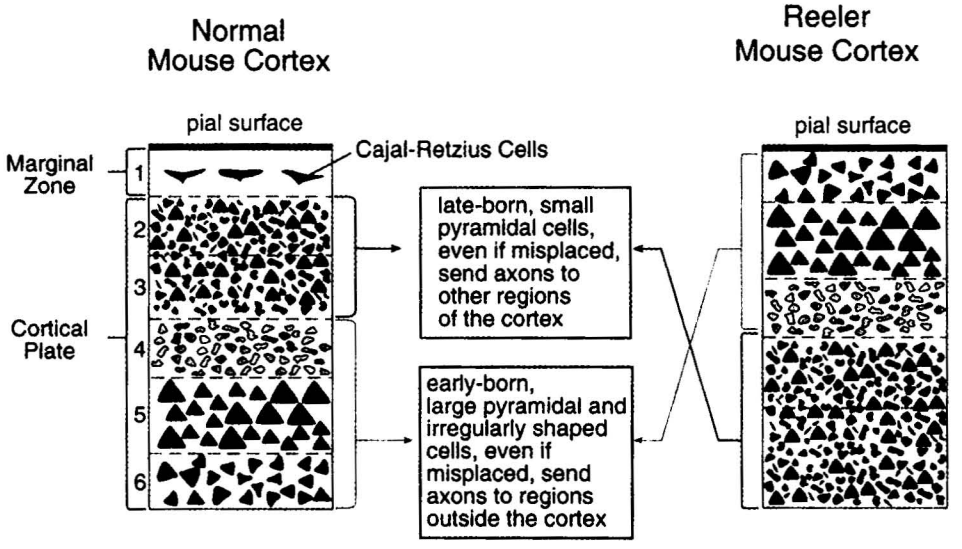

Fig. 1 The normal pattern of cortical development is shown on the left. The cerebral cortex develops into six layers, with the earliest-born neurons lying in the deepest layers and the late-born neurons migrating to more superficial layers. In the cerebral cortex of the *reeler* mutant, this pattern is reversed. The protein that is mutated in this disorder is normally secreted into the extracellular space and is believed to act as a signal to migrating neurons. Adapted from Alberts B, Bray D, Lewis J, Raff M, Roberts K, Watson J (1994), *Molecular Biology of the Cell*, New York: Garland Publishing, p. 1111.

pheral nervous systems. The binding of these extracellular proteins to proteins on the leading edge of a growing neuron is thought to transmit a signal into that neuron indicating it is on the proper migratory route.

Reelin may play a similar key role in regulating neuronal migration in the cortex and cerebellum. Migrating neurons move toward the cortical surface along glial shafts until they come in contact with the reelin protein. At this point, the neurons detach from the glial surface and stop their migration. They then extend their axons and dendrites and make synaptic connections. Similar signaling proteins are likely to be found in other regions of the brain. These proteins provide the cues that migrating neurons need to stop their wandering and begin the development of synaptic connections with their target neurons. It is intriguing to speculate that subtle mutations in these proteins might contribute to developmental disorders such as specific learning disorders. More extensive mutations might be associated with severe disorders such as schizophrenia and autism.

WEB SITE OF INTEREST

http://www.ucalgary.ca/~browder

ADDITIONAL READINGS

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