EDITORIAL

Neural Development: Mysterious No More?

Until recently, the mechanisms by which a fertilized egg develops into a complex organism were almost as mysterious as the mechanisms by which we think and talk—but no longer. The shroud of mystery surrounding development has been peeled away so effectively that an eminent developmental biologist wrote earlier this year that the principles of development are understood and all that remains is to fill in the details.* This view may be overly optimistic, but it reflects the growing feeling that we are racing toward a detailed molecular understanding of how we develop. Although the nervous system is uniquely complex and uses some developmental processes seen in no other systems, much of its development is similar to that of other organs, and the rate of progress in developmental neurobiology has been at least as great as that in developmental biology in general.

Two major advances are largely responsible for both the recent progress and current optimism. First, recombinant DNA technology has made it possible to identify every gene and protein in an organism and to manipulate them in order to explore their functions. Second, it has been discovered that the molecular mechanisms of development have been conserved during animal evolution to a far greater extent than had been imagined. This conservation means that discoveries about the development of worms and flies, which come from the kinds of powerful genetic studies that are not possible in mammals, greatly accelerate the rate at which we can discover the mechanisms and molecules that operate during our own development.

Neural development follows a similar pattern in most animals. First, a group of cells acquires the potential to become neural cells, and some commit to a neural fate. These precursor cells then develop into the types of neurons and glial cells that are appropriate to their positions along the body axes. At each step, complex interactions among cells, as well as intracellular programs that reflect the cell's history, influence the choices a cell makes. With each choice, new sets of genes are switched on while others are switched off. After a neuron forms, it often migrates to a new location and extends an axon toward its target. The crawling growth cone at the tip of the developing axon must find its way to the appropriate target region, guided by molecules that act as attractants or repellents—some soluble, some bound to the extracellular matrix, and some bound to the surface of cells. Once in the correct region, the axons branch and their terminals make synaptic connections with selected target cells. Two sequential pruning processes then fine-tune these initial neuronal networks—one causing the loss of entire neurons and the other the loss of axonal branches and synapses. Both seem to involve competition for limited amounts of specific trophic signals released by the target cells. In the first process, neurons that fail to get enough trophic signals from their target cells undergo programmed cell death. This eliminates neurons that have made inappropriate connections and helps match the number of neurons to the number of target cells. In the second process, the connections between surviving neurons are refined by the removal of some axonal branches and their synapses and the stabilization of others, by a process that depends on electrical activity along the axons and competition among neighboring nerve terminals for trophic signals released by target cells. Even in the mature nervous system, synaptic connections are modified by use. Many of these synaptic changes also seem to depend on trophic signals released by target cells.

The main progress made in developmental neurobiology in the past 5 years or so has been the identification of many molecules, both extracellular and intracellular, that are involved in these various processes. A fine sampling of this progress is provided in this special issue by some of the main protagonists. It is tempting to think that the main principles of neural development will have been discovered by the end of this century and that the cellular and molecular basis of the mind will be the main challenge for the next. An alternative view is that this feeling that understanding is just a few steps away is a recurring and necessary delusion that keeps scientists from dwelling on the extent of the complexity they face and how much more remains to be discovered.

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*L. Wolpert, *Curr. Biol.* **6**, 2 (1996).