Recognition Molecules Are Trailblazers for Axon Pathways

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Issue: *Neurons do not stop making or revising synapses at birth, and many may continue these processes throughout adulthood. Neurotrophic growth factors may signal an axon to sprout, and then recognition molecules blaze the pathway for the growing axon by attracting it in one direction while repelling it from another.*

Last month's BRAINSTORMS feature reviewed the neurotrophic factors that regulate neuronal survival as well as the sprouting of axons to form new connections.[1] Here we discuss the recognition/guidance molecules that direct these sprouting axons along their journey within the brain to help them form connections with their targets of communication.

The Immature Brain: Recognition Molecules

During development, molecules in the immature brain can cause axons to cruise all over the brain, following long and complex pathways to reach their correct targets.[2–4] Neurotrophins can induce neurons to sprout axons by having them form an axonal growth cone. Once the growth cone is formed, neurotrophins as well as other factors make various recognition molecules for the sprouting axon, presumably by having neurons and glia secrete these molecules into the chemical stew of the brain's extracellular space.[1–4]

These recognition molecules can either repel or attract growing axons, sending directions for axonal travel like a semaphore signaling a navy ship.[2–4] Indeed, some of these molecules are called *semaphorins* to reflect this function. Once the axon growth tip reaches port, it is told to collapse by semaphorin molecules called collapsins, allowing the axon to dock into its appropriate postsynaptic slip and not sail past it. Other recognition molecules direct axons away by emitting repulsive axon-guidance signals (RAGS).

The Maturing Brain: Growth and Destruction

As brain development progresses, the distance that axonal growth cones can travel is greatly impeded, but not completely lost. The fact that axonal growth is retained in the mature brain suggests that neurons continue to alter their targets of communication, perhaps by repairing, regenerating, and reconstructing synapses as demanded by the evolving duties of a neuron. A large number of recognition molecules supervise this. Some of these are listed in the Table, and include not only semaphorins/collapsins, but also molecules such as netrins, neuronal cellular adhesion molecules (NCAMs), integrins, cadherins, and cytokines.[2–4]

During brain development, not only an excess of neurons is made, but also an excess of synapses. Prenatally, axons run wide and far throughout the brain. By birth, however, about 90% of neurons are apoptotically destroyed by neurotrophins. The 10% that are left still number roughly 100 billion. Then, at adolescence, the brain destroys between 30% and 50% of its synaptic connections among the remaining neurons.[5] This leaves an average of 10,000 individual connections between neurons. Apoptosis[6] as well as excitotoxicity[7] may mediate such neuronal cell loss and pruning of synaptic connections.

Hypothetically, if the brain makes the wrong decisions about which neurons should commit apoptotic mass suicide, or which synapses to massacre during adolescence, a neurodevelopmental disorder, ranging from mental retardation to attention deficit, may result. Also, profound experiences, whether positive nurturance or traumatic abuses, may shape the se-

BRAINSTORMS is a monthly section of The Journal of Clinical Psychiatry *aimed at providing updates of novel concepts emerging from the neurosciences that have relevance to the practicing psychiatrist.*

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Take-Home Points

- Axons can sprout and form new connections, not only in developing brains but also in mature brains
- Numerous recognition molecules that direct and modify such neuronal plasticity have been discovered
- Understanding how to coordinate axonal sprouting with appropriate guidance to desired target sites may enhance learning, facilitate psychotherapy, and even counteract the effects of neuronal inactivity during aging

lection of neurons and synapses. Perhaps abnormal pruning of synapses plays an especially important role in disorders that have onset around adolescence, such as schizophrenia.[8]

The Mature Brain: Remodeling and Stabilization

After the dramatic reduction in neurons and synapses is complete, activity calms down considerably in the mature brain, where maintenance and remodeling of synapses continue in modest amounts and over more limited distances. This may provide the substrate for learning, emotional maturity, and the development of cognitive and motor skills throughout a lifetime.

Table. Recognition Molecules

PSA-NCAM: polysialic acid-neuronal cell adhesion molecule
NCAM: neuronal cell adhesion molecules such as H-CAM, G-CAM,VCAM-1
APP: amyloid precursor protein
integrin
N-cadherin
laminin
tenscin
proteoglycans
heparin-binding growth associated molecule
glial hyaluronate binding protein
clusterin

Although the continuous structural remodeling of synapses in the mature brain, directed by recognition molecules, cannot approximate the pronounced long-range growth of early brain development, it could be beneficial, in part, because it simultaneously allows structural plasticity while restricting unwanted axonal growth. This would stabilize brain function in the adult and could, furthermore, prevent chaotic rewiring of the brain by limiting both axonal growth away from appropriate targets and ingrowth from inappropriate neurons.

On the other hand, the price of such growth specificity becomes apparent when a long-distance neuron in the adult brain dies, thus making it difficult to reestablish original synaptic connections, even if axonal growth is turned on. For this reason, getting a cortical neuron to reinnervate the thoracic spinal cord after injury is currently an impossible task in the mature nervous system. Figuring out how to make the right axons active—no matter how far away—without producing an axonal free-for-all is the task of therapies that enhance CNS repair. Replicating the desired signals with neurotrophic factors and then steering the axonal sprouts with recognition molecules is a theoretical therapeutic possibility. The exciting possibilities for therapeutic applications of neurotrophic factors and recognition molecules in both neurodegenerative and neurodevelopmental disorders will be discussed in next month's BRAINSTORMS. ◆

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