Development, degeneration and regeneration of neuronal circuits

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The brain is the most complex organ in the body. It is the seat of perception, cognition, and the control of movement; it makes us who we are. These many remarkable functions of the brain are determined by the hundred billion nerve cells (or neurons) that make up the brain, and by the network of highly specific connections among these cells. This pattern of connections arises during embryonic development when each neuron sends out a thin extension called the axon that navigates through the embryonic environment to reach its targets and form connections at synapses. The neuronal axon can branch, enabling each neuron to connect to multiple targets – on average, over a hundred for cortical neuron connections to cortical targets.

The functioning of the brain is dependent on the precision of these connections and their integrity. Miswiring of the brain during development can lead to neurological syndromes. In neurodegenerative disease, synapses are lost and axons degenerate, interrupting the circuits and leading to dementia or motor disorders such as Parkinson's disease. Following injury, such as stroke and spinal cord injury, axons are severed leading to paralysis and other dysfunctions; axons must regrow to regenerate connections.

Over the past two decades, significant progress has been made in identifying the molecules and mechanisms that determine the development, degeneration and regeneration of neuronal connections. The first three lectures in this series summarized this progress, with special reference to our own work on these topics. The fourth lecture discussed the prospects for translating these basic science discoveries into therapies for neurological disorders by the biotechnology and pharmaceutical industries.

Lecture 1: Assembling the brain: the logic and mechanisms of neuronal guidance

In the embryo, extending axons are guided by chemoattractive and chemorepulsive molecules. This lecture reviewed the discovery of the molecules that mediate these guidance effects. In the 1990s, four canonical guidance cue families were discovered: the Netrins, Semaphorins, Ephrins and Slits. These molecules are evolutionarily conserved and can be bifunctional, attracting some axons and repelling others. Two other important families of cues are morphogens (members of the Hedgehog, Wnt and BMP families) and growth factors. Other cues continue to be identified, including members of the immunoglobulin superfamily, but we have yet to account for the guidance of any axon from its site of origin to its target, suggesting that our knowledge of these cues is still incomplete. Mutations in genes coding for guidance molecules are now known to underlie several familial neurological disorders.

To extend long distances, axons must navigate a series of intermediate targets. For each target, the axon is initially attracted, but when it reaches the target it switches its response and becomes repelled, allowing it to move on to the next leg of its trajectory. The mechanisms enabling axons to switch from attraction to repulsion at intermediate targets remain poorly understood, but are

among the most hotly pursued in the field as they will provide a window onto plasticity mechanisms that might be useful for neuronal repair.

Lecture 2: Rewiring the brain: mechanisms to promote neuronal regeneration

In spinal cord injury, axons connecting the brain to the spinal cord are severed, leading to to paralysis. This paralysis is often permanent because axons in the brain and spinal cord (the central nervous system, or CNS) fail to regenerate, at least in higher vertebrates, including humans; in amphibians and fishes some CNS regeneration can occur. The mechanisms that prevent regeneration remain poorly understood. Neurons in the peripheral nervous system (PNS) do regenerate, but this requires the activation of an embryonic-like growth program in these neurons. This lecture reviewed progress in identifying this molecular program, which, if activated in CNS neurons, might help stimulate regeneration. Regeneration is also blocked by inhibitory factors in the environment, which are being actively sought. The lecture described recent data suggesting that axon guidance molecules that function in the embryo might be redeployed to block regeneration, providing interesting therapeutic targets to stimulate repair.

Lecture 3: Neuronal self-destruction and neurodegenerative disease.

During embryonic development, axons are made in excess and must be pruned, which occurs via a degenerative mechanism. The molecular basis of this degeneration remains poorly understood. Previous studies had suggested that the mechanisms within the axons that mediate degeneration are very distinct from those operating during death of neuronal cell bodies. This lecture questioned those data, describing more recent studies suggesting the involvement of a canonical cell death module involving Bax and caspase effectors, but with some minor differences. Mechanisms that trigger degeneration upstream of this module were also discussed, with an emphasis on the involvement of the canonical axon guidance molecules as prodegenerative triggers – another unifying theme. The lecture concluded with a discussion of a degeneration mechanism operating in the embryo that involves the Amyloid Precursor Protein (APP), a causal factor in Alzheimer's disease. This finding suggests that embryonic and adult degeneration may involve overlapping mechanisms. The advances described here are suggesting novel entry points for therapeutics for neurodegenerative disease.

Lecture 4: The biological revolution, molecular medicine, and the future of biotechnology

The explosion of knowledge in basic biological sciences in the past two decades has in turn led to an acceleration in our understanding of human disease mechanisms. This knowledge is now being exploited to develop drugs for poorly treated diseases. This lecture described how our knowledge of cancer was the first to break open, starting in the early 1990s, and how this knowledge has fueled the development of hundreds of cancer medicines now in clinical trials. Other fields are breaking open sequentially, including immunology, infections diseases, and metabolism. Neuroscience is lagging, with some progress in understanding neurodegenerative disease but less understanding of psychiatric disorders. The challenges in harnessing this new knowledge by industry were discussed. A model of science-driven drug discovery provided by the Genentech Research organization was given as a model for how such drug discovery can be successful.