

Lecture 10 -- Glial Cells and Neuronal Injury - Mason

I. RESPONSE OF THE NEURON TO INJURY

- A. All neurons react similarly
- B. Principles
 1. If cell body damaged, the neuron dies and is not replaced by cell division in mature brain.
 2. If axon damaged or severed, again, the neuron is often lost, but there is a good chance of regeneration, primarily in the PNS. Occasionally, there is regrowth of axons in the CNS.

II. GLOSSARY OF GLIAL CELLS

- A. Astroglia – in adult, thought to block regeneration, especially "reactive" astroglia in scars near injury site; in the immature nervous system, they support axon growth
- B. Myelin-forming cells: oligodendroglia (oligodendrocytes) in CNS, Schwann cells in PNS.
Dichotomy in CNS vs. PNS: oligodendrocytes are inhibitory to axon regrowth in adult CNS regeneration; Schwann cells are growth supportive - as a growth surface and by releasing growth factors.
- C. Microglia (resting) and macrophages (active) - cells of immune system. Like astroglia, not clear whether they aid in growth support as well as phagocytose; not well-understood.

III. DEGENERATION

- A. Cytological signs.
 1. Immediate
 - a. Synaptic transmission off
 - b. Cut ends pull apart and seal up, and swell because, within the axon, axonal transport carries molecules and organelles both anterogradely and retrogradely
 - c. Degeneration of the axon terminal or synaptic ending; accumulation of neurofilaments and vesicles.
 - d. Glia normally surround terminal but, after axotomy, help to pull terminal away from target cell.
 2. Days to weeks
 - a. Myelin breaks up and leaves debris (hard to degrade).
 - b. Axon itself undergoes Wallerian degeneration
 - c. Chromatolysis - cell body swells; Nissl substance and eccentric nucleus.
- B. Severing the axon causes degenerative changes in the injured neuron and in the cells that have synaptic connections with that neuron.
 1. Visual system model
 2. Classical use of this approach – transynaptic degeneration - to delineate neural circuitry.

IV. REGENERATION

- A. Neurons in the PNS can regenerate their axons. How?
 1. Schwann cell helps in regeneration of cut distal axon; the postsynaptic cell, if not injured, can provide trophic factors
 2. Axon distal to cut degenerates but Schwann tubes remain and are rebuilt.
 3. Axons sprout in many directions, some find Schwann cell tubes of the distal stump.
 4. Macrophages clean up degenerated myelin and debris.
- B. Neurons in the CNS have a limited capacity to regenerate axons. Why?

Growth is impeded by the negative elements in the environment and by the lack of intrinsic growth proteins. *PNS neurons cannot grow in the CNS.*

1. Extracellular growth-promoting molecules, such as laminin, have limited or different distributions in adult CNS compared to developing brain; there is a correlation between levels of proteoglycans and success of regeneration.
2. Growth factors/neurotrophins have different spatial distributions and activity in mature CNS
3. Intracellular growth-promoting molecules, e.g, GAP-43, a membrane-associated protein involved in signal transduction at the growing tips of axons, are at low levels compared to developing CNS
4. Factors on oligodendrocytes inhibit axon growth in the mature CNS
5. Glial cells, including astroglia and microglia, proliferate near a wound, and unlike immature forms, block axon growth in mature CNS; role of microglia unclear, however.

Thus, upon injury to the CNS, there is an imbalance of growth-promoting and growth-inhibiting factors, in favor of the latter. Adult CNS neurons can regrow, but the environment is inhospitable.

V. EXPERIMENTAL STRATEGIES TO PROMOTE REPAIR/RECOVERY OF FUNCTION IN CNS

A. Therapeutic strategies/principles

1. Peripheral nerve bridges, a natural transplant for nerve regrowth
2. Cellular transplants
 - a. Fetal tissue, or stem cells, to replace dead or injured neurons
 - b. "Good" glia: olfactory ensheathing glia (OEG)
 - c. (Cell lines/*transfected* cells that produce growth factors)
3. (Gene transfer via retroviruses, injection of RNA, anti-sense oligonucleotides)
4. Direct delivery of growth factors
5. Application of "neutralizing" activity (e.g. antibodies) to combat inhibitory glia/myelin

B. Recent advances in regeneration

1. Vaccination against myelin
2. "Prime" cells with neurotrophins or cyclic nucleotides: neurons become insensitive to myelin proteins and can better regenerate
3. Microglia and the injuring the lens in the eye
4. Identification of oligodendrocyte-inhibiting factors – "– MAG (myelin-associated glycoprotein), NOGO, Omgp (Oligodendrocyte myelin glycoprotein).and their receptor(s)

Relevant reading: Chapters 2 and 55 in "Principles"

Qiu J, Cai D, Dai H, McAtee M, Hoffman PN, Bregman BS, Filbin MT. Spinal axon regeneration induced by elevation of cyclic AMP. *Neuron*. 2002 34(6):895-903.

Wang KC, Kim JA, Sivasankaran R, Segal R, He Z. P75 interacts with the Nogo receptor as a co-receptor for Nogo, MAG and OMgp. *Nature*. 2002 420(6911):74-8.