Lesson (1)

The cellular organization
of the nervous system
(neuroglia)

The neuroglia: structure and functions

There is a debate on their actual number (formerly 10 times):
now 2-3 times the number of the neurons

5 main types:
- Astrocytes
- Ependimal cells
- Oligodendrocytes
- Schwann cells
- Microglia

Functions:
- Filter (Blood-Brain Barrier)
- Physical support
- Protection (sequestration of ion or neurotransmitters in excess; resident immune system)
- Trophic and metabolic support
- Signal transduction (transcytosis, myelin formation)
- Regeneration and degeneration/scar formation (neural stem cells)
What are glia?

Neuroglia="nerve glue" (Virchow, 1859)

Glia as cells: S. Ramon y Cajal, P. del Rio-Hortega, 1900-1920

**TABLE 2.2. Types of Vertebrate Glial Cells**

<table>
<thead>
<tr>
<th>Type</th>
<th>Appearance</th>
<th>Features and Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astroglia</td>
<td>Star-shaped, symmetrically nutritive and support function</td>
<td></td>
</tr>
<tr>
<td>Microglia</td>
<td>Small, macrophage derived, defensive function</td>
<td></td>
</tr>
<tr>
<td>Oligodendroglia</td>
<td>Asymmetrical: form myelin around axons in brain and spinal cord</td>
<td></td>
</tr>
<tr>
<td>Schwann cell</td>
<td>Asymmetrical: wraps around peripheral nerves to form myelin</td>
<td></td>
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</tbody>
</table>

A spatial view of neuroglial Cells of CNS
THE NEUROGLIA:

some FUNCTIONS

• Astrocytes & Ependimal cells: Blood brain barrier, support, trophic, signalling, support, homeostasis
• Oligodendrocytes \( \text{Support & myelin, signalling} \)
• Schwann Cells
• Microglia: resident immune system
Astrocyte/capillary interactions: foot process

Two types of astrocytes

- Protoplasmic (pedunculated) in the grey matter
- Fibrous in the white matter

Pedunculated astrocytes  Fibrous astrocyte in the cerebellum white matter

Figure 9-11
Astrocytes (astroglia) “star-cells”

Most numerous cell type in brain
Constitute ~30-50% of brain volume

NORMAL FUNCTIONS
- **Developmental**: Migrational and Axon guidance of neurons
- **Trophic** support of neurons (growth factors)
- **Homeostasis** of neuronal microenvironment
- **Ionic**
- **Metabolic**
- Neurotransmitter uptake
- **Blood-Brain barrier**: induction and maintenance
- **Synaptogenesis** and synaptic remodeling

Astrocytes contact virtually every cell component in brain

- Other astrocytes (gap junctions)
- Ependymal cells
- Neurons (somas, processes, synapses)
- Oligodendroglia
- Capillary endothelial cells
Astrocytes

Trophic function:
produce growth factors/neurotrophic factors (NGF, BDNF, GDNF, CNTF, FGFs), especially in development and regenerative responses to injury

Buffer extracellular space to maintain homeostasis for neuronal function:
• K+ spatial buffering
• Protect neurons from excitotoxicity: active glutamate uptake/conversion to glutamine (cycled back to neurons)

Astrocytes communicate with each other, other glia, and neurons via intercellular calcium waves mediated by GAP-junctions and extracellular signals

Calcium Waves in Retinal Glial Cells
Eric A. Newman and Kathleen R. Zahs
Science 1997 February 7; 275: 844-847.
Glia work in unsuspected ways: synaptic depression after glia contacts synapses

How did they figure this out?
(or, what does it take to get a paper in Nature?)

• Observation:
  – Cultured neurons formed Ach synapses
  – When glia were allowed to contact synapses, synaptic depression was observed

• Question:
  – How do the glia sense and respond to the Ach to modulate transmission?

• Finding:
  – It senses Ach by AchBP (identified by Bungarotoxin purification scheme, partial AA sequence)

• Response:
  – Glia have nAChR, which senses increased Ach and induces release of AchBP from glia into the cleft, suppressing transmission (negative feedback).
Who are the stem cells of the adult brain?

**astrocytes vs. ependymal cells**

The subventricular zone

**Ependymal cells**


Dr Arturo Alvarez-Buylla and Dr Jonas Frisen report discovering site in brain of elusive neural stem cell, founding cell from which perhaps whole brain develops, but each scientist has a different site in mind; Frisen contends that neural stem cells are cells that line ventricles, while Buylla contends neural stem are the star-shaped cells called astrocytes that lie one layer in from ventricle lining; experts say their contradictory findings may yet be reconcilable.

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**Astrocytes control synapse formation**

- **No GLIA**
  - Synaptotagmin
- **Plus GLIA**
  - PSD-95

Control of Synapse Number by Glia

Erik M. Ullian, Stephanie K. Sapperstein, Karen S. Christopherson, and Ben A. Barres
Astrocytes in disease: gliosis

Astrocytosis/gliosis

= response of astrocytes to many forms of injury: trauma, inflammation, MS, infection, neurodegeneration

MS plaque: GFAP

Astrocytes-gliosis

Classical description of gliosis is:
- hypertrophy,
- +/- proliferation,
- Prominent expression of intermediate filaments: “Glial filaments”:
  - Glial Fibrillary Acidic Protein (discovered as a major component of Multiple Sclerosis White Matter Plaques)
  - Also, vimentin, nestin

Reality: there must be many distinct forms of astrocyte activation; hundreds or thousands of distinct changes in gene expression
More reactive astrocytes (gliosis)

BBB=endothelial tight junctions
Ependymal cells

- Line ventricles of brain and spinal cord canal
- Ciliated, columnar epithelium, with cilia and adherens junctions; but express glial markers
- May extend cytoplasmic processes into brain parenchyma
- Recent controversy as to whether Ependymal cells (versus subependymal astrocytes) are adult neural stem cells
Ependymal cells

Chroiod plexus
Oligodendroglia (CNS)

• “few-branch” glia
• Discovered by del Rio-Hortega, using metallic impregnation techniques in 1921
• one oligo myelinates many CNS axons
• CNS myelinators (white matter)
• Target of autoimmune attack in MS
• Specific oligodendrocyte myelin proteins:
  – PLP
  – DM20
  – MBP
Ultrastructure of white matter

Oligodendroglia

1 glial cell forms myelin around many axons

Figure 9-13
Schwann Cell (PNS)

Schwann Cell

• Theodore Schwann (19th cent. German anatomist; a key founder of cell theory)

• Each Schwann cell wraps a portion of a single peripheral axon
Myelinated peripheral axons

- Myelin acts as an insulator for vertebrate nerve cells
- Cellular structure - myelin is composed of alternating layers of protein and lipid (20% protein and 80% lipid; looks white)
- Very little cytoplasm between layers
- Myelin represents a major vertebrate feature
  - Not a major factor in invertebrates nervous systems
  - Major advantages
    - Faster conduction (10x)
    - Smaller sized neurons (10x)
Myelin 2

- Oligodendrocytes in CNS and Schwann cells in PNS
- Oligodendrocytes in CNS myelinate several fibers
  - myelination spirals inward with new layers pushed under the older ones
- In CNS - no neurilemma or endoneurium
- In PNS, hundreds of layers wrap axon
  - the outermost coil is schwann cell (neurilemma)
  - covered by basal lamina and endoneurium
- Gaps between myelin segments = nodes of Ranvier
- Initial segment (area before 1st schwann cell) and axon hillock form trigger zone where signals begin

Myelin Sheath

- Note: Node of Ranvier between Schwann cells
Myelination in PNS

- Myelination begins during fetal development, but proceeds most rapidly in infancy.

Unmyelinated Axons of PNS

- Schwann cells hold small nerve fibers in grooves on their surface with only one membrane wrapping
Myelination in CNS

- Diameter of fiber and presence of myelin
  - large fibers have more surface area for signals
- Speeds
  - small, unmyelinated fibers = 0.5 - 2.0 m/sec
  - small, myelinated fibers = 3 - 15.0 m/sec
  - large, myelinated fibers = up to 120 m/sec
- Functions
  - slow signals supply the stomach and dilate pupil
  - fast signals supply skeletal muscles and transport sensory signals for vision and balance
**Impulse Conduction - Unmyelinated Fibers**

- Voltage-gated channels needed for APs
  - fewer than 25 per \( \mu \text{m}^2 \) in myelin-covered regions
  - up to 12,000 per \( \mu \text{m}^2 \) in nodes of Ranvier
- Fast \( \text{Na}^+ \) diffusion occurs between nodes

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**Saltatory Conduction - Myelinated Fibers**

- Voltage-gated channels needed for APs
  - fewer than 25 per \( \mu \text{m}^2 \) in myelin-covered regions
  - up to 12,000 per \( \mu \text{m}^2 \) in nodes of Ranvier
- Fast \( \text{Na}^+ \) diffusion occurs between nodes
Peripheral Nerve (Fascicle)

- Perineurium
- Endoneurium
- Myelinated axons

Peripheral nerve

- Spinal cord
- Sensory ganglion
- Dorsal root
- Ventral root
- Cell body of motor neuron
- Interneuron
- Motor neuron
- Striated muscle
- Sensory neuron
- Schwann cell
- Myelin
Neuropathological note

- Tumors of the nervous system are largely Glial tumors:
  - Peripheral: Schwannoma, Neurofibroma
  - Central:
    - astrocytomas (includes benign pilocytic astrocytic and most common and most malignant: glioblastoma multiforme)
    - Oligodendroglomas
    - ependymomas

Multiple Sclerosis is an autoimmune attack on white matter
Major proteins found in Myelin

- **P0 (protein zero)** intraperiod line formation
  - a glycoprotein only in myelin-forming Schwann cells (50%)
  - similar to CAMs, but bifunctional (in PNS)
- **proteolipid protein (PLP)** intraperiod line formation
  - only in Oligodendrocytes (50%) (in CNS)
- **myelin basic protein (MBP)**
  - expressed in both, involved in compaction
  - very antigenic, can be used to induce experimental multiple sclerosis, (T-lymphocyte inv. of CNS and PNS
  - **shiverer** in mice
- **NCAM**
  - Cellular adhesion

How these proteins work together
Schwann Cells and Peripheral Neuropathies

- Schwann cells also perform trophic functions (NGF production in regeneration).
- Myelin proteins
  - Schwann cells (PNS): P0, PMP22
    - CMT1A = duplication of PMP22
    - HNPP = deletion of PMP22 (surprisingly, deletion causes milder phenotype than CMT1A (duplication))

Radial glia

- Embryonic scaffold throughout CNS
- Guides for radial migration of neurons
- Produce matrix and adhesion proteins
Radial glia

- Adult: radial glia persist in cerebellum (Bergmann glia) and in retina (Muller cells)

Gliogenesis

Note the absence of microglia from this family tree!
Microglia: OX-42
Microglia (as opposed to Macroglia=astrocytes, oligos)

- Most like tissue macrophages elsewhere in body; not of neuroectodermal origin, like all macroglia
- Chief mediators of immune responses in brain
- CNS is not completely isolated from immune reactions
- Microglia derive from marrow monocyte lineage
- Have phenotypic markers similar to tissue macrophages:
  - CD68, HAM-56, IL-1alpha,beta, class II MHC, OX-42

Microglia

- Most roles for microglia in context of CNS pathology; little known yet about normal functions. Examples of possible normal function are developmental: phagocytosis of apoptotic neurons; secretion of factors
- Activated microglia can produce and secrete cytokines capable of activating astrocytes: e.g. IL-1; some think microglia are the primary sensors of CNS damage.
- Some say that they have no function in the healthy adult brain: They don’t form a network with intercellular junctions, as do neurons and astrocytes

LIKE BODYGUARDS: THEY JUST SIT THERE WAITING FOR AN INSULT
Microgliogenesis

How do we know this is true?

Microglial activation
**Microglia**

**Blood-brain Barrier**

[Diagram showing microglia and blood-brain barrier]