Neurons
(and glial cells)

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Human Brain

Grey matter

White matter
Golgi Stain

He mistakenly left brain sample in silver stain overnight. Next day he looked at slices of brain under a microscope and saw these cells which are neurons.

Camillo Golgi
Cajal

Cajal used Golgi stain to describe the structure of neurons and define axons and dendrites.

Genetically encoded dyes (GFP and variants) can be used to label individual neurons.
Genetically encoded dyes

Brainbows

An example of expressing differently colored protein dyes in neurons. Allows one to visualize distinct neurons and examine their connections.

Jeff Lichtman
Neurons have a variety of shapes

Cajal found that neurons have a variety of shapes. Researchers are trying to determine how the expressions of different genes generate these unique cellular shapes.
Neurons: Cell body with axon and dendrites. Dendrites are extensions of cell body have most of the components that are found in the cell body. Dendrites receive input from other cells. Axons are more specialized. Usually only one axon per neuron, but they can branch. Neurons in culture will develop axons and dendrites in the absence of other cells but require growth factors.

Stages of axonal development (in vitro)

1. Lamellipodia
2. Minor Processes
3. Axonal Outgrowth
4. Dendritic Outgrowth
5. Maturation

Dotti and Banker

axon (typically only one)
Axon and dendrites have different properties

Axons and dendrites have different molecular compositions as shown by this image of a neuron in culture. Note that the axon synapses onto one of the dendrites from the same cells.

Red: axonal marker
Green: dendritic marker
Both dendrites and axons can be extremely branched. Axons are typically longer (can be much longer).

Axon and dendrites of a single neuron.

Inhibitory interneuron (dendrites blue, axon red) shown adjacent to a schematic of a hippocampal pyramidal neuron.
Neurons are organized in neuronal circuits

Schematic diagram of the neuronal circuit mediating tail and siphon withdrawal reflex in Aplysia (an invertebrate organism)

Key compartments of the neuron:

cell body (soma, perikaryon)
dendrites
axons
Neuronal perikarya

Cell bodies of neurons can be very large. Must support long, branched axons and dendrites. Neurons last for life of organism. Most organelles in cell bodies extend into dendrites (e.g., ER). Axon is more selective about which organelles can enter from the cell body. All protein synthesis machinery is in cell body or dendrites. Axons can make lipid but lack protein synthesis machinery.

Motor Neurons
Ventral Horn
Dendrite

Most organelles of the cell body extend into the main dendritic branches

Nissl substance = RER

Axon hillock

Cell body or perikaryon

blood capillary
Entry of organelles in axons is selective. There are no rough endoplasmic reticulum or ribosomes (and thus no protein synthesis) and Golgi complex in mature axons.

Nissl substance = RER

Axon hillock
Dendrites integrate inputs from many different axons (can receive 1000s of inputs). Each synapse contributes a small amount of depolarization of the neuron. If the sum of the signals is sufficient, an action potential will be triggered in the axon.
Golgi complex

RER

Ly
Golgi complex

Silver impregnation
(From Camillo Golgi)

immunofluorescence

Golgi complex extends into dendrites but not axons.
The length of the axons poses special needs:

- Structural support
- Assisted organelle transport
- Local synthesis and degradation of metabolites
- Signal propagation

Axons can be extremely long compared to the cell body. Neurons need deliver machinery down the axon. Need structural support both internally (cytoskeleton) and externally. Neurons deliver signals via their axons to specific cells, similar to phone cables that make specific connections. Because axons make specific contacts, few different types of neurotransmitters are used.
Axons are surrounded by glial cells.

Unmyelinated Axons

Microtubule

Glia cells provide external support to axons. Microtubules and neurofilaments, a type of intermediate filaments provide internal support.
Axons are surrounded by glial cells

Myelinated axon

Myelin sheath wraps axons

Schwann cells (PNS)
Oligodendrocytes (CNS)
Myelin

Development of myelin

Node of Ranvier

Gaps in myelin sheath are created where adjacent glia cells meet on the axon. These gaps are called nodes of Ranvier.
Myelin

Development of myelin

Node of Ranvier
Node of Ranvier, EM
Node of Ranvier

Myelin prevents depolarization of membrane but nodes contain sodium channels. Action potential jumps from node to node generating fast, saltatory conduction.

Nodes of Ranvier

mutation: quivering mouse
A prominent cytoskeletal scaffold

Cytoskeleton provides structural support and creates tracks for transport of cellular material.

Myelinated Axon longitudinal-section

Quick-freeze-deep-etch view From Hirokawa
Axonal transport

- Anterograde, slow 2-4 mm/day
  - cytosolic proteins, cytoskeletal elements…
- Anterograde, fast (kinesins) 100-400 mm/day
  - organelles, particles

- Retrograde, fast (cytoplasmic dynein)
  - organelles, particles (retrograde signaling, targeting to lysosomes)
Organelle transport
(microtubular motors in axonal cytoplasm)

From Paul Forscher

From Nabutaka Hirokawa
Microtubular motors: kinesin(s) and cytoplasmic dynein

Different types of kinesin are responsible for transporting different kinds of cellular organelles.

A multiplicity of kinesins (different cargo vesicles)
Weiss axoplasmic flow

Proximal to axonal block Distal to axonal block

From Tsukita and Ishikawa

Axonal block

Newly made material accumulates on proximal side of block

Old material accumulates on distal side of block.
A continuous smooth ER from the cell body to axon terminal

Several forms of hereditary spastic paraplegias are due to mutations in proteins that control the shape and the dynamics of the ER.
Signal propagation in axons
Unmyelinated nerve

Conduction 0.6-2 m/sec

Na+ channel

gradient of Na+ and K+ across the plasma membrane is maintained by Na+/K+ ATPase
Signal propagation in axons

Myelinated nerve

Conduction 5-120 m/sec

Saltatory conduction

nodes of Ranvier
Growth cones

Guide growth and development of axons. Are attracted to and repulsed by specific chemicals that guide the direction of their growth.

attraction/repulsion

DIC

Microtubules

Lab of Paul Forscher

Actin filaments

Elke Stein
Growth Cone

Lab of Paul Forscher, Yale
Axonal Degeneration and Regeneration

Axon regeneration occurs in the peripheral nervous system but does not occur in the white matter of the central nervous system.

Myelin made by Schwann cells inhibit growth of axons in CNS. Prevents overgrowth of axons to maintain fidelity of connections.

white matter  gray matter
Model organisms

tools to study principles in neurons and circuits development

*Caenorhabditis elegans*

302 neurons (instead of billions as in the human brain)

Colon Ramos lab

AIY neurons

*wild type*  *daf-18 mutant*
Axonal Regeneration

Axotomy

Regeneration

Lab of Marc Hammarlund, Yale CNNR
Glial cells
Glial cells
Glial cells

ASTROCYTES

- Structural support
- Physical isolation of neurons
- Buffer of extracellular ions (f.e. sink for K+)
- Uptake/clearance of neurotransmitters
- Metabolic functions to support neurons
- Secretion of growth factors
- Response to injury
- Blood-brain barrier
Astrocyte
Radial glia tracks for neuronal migration during brain development

from F. Polleaux
Myelin generating cells: Oligodendrocytes (CNS) & Schwann cells (PNS)

Schwann cells = peripheral nervous system

Oligodendrocytes = central nervous system
Multiple Sclerosis (MS)

1. Inflammation
2. Demyelination
3. Impairment of nerve conduction
4. Neurological deficits

Macrophage engulfing myelin in experimental autoimmune encephalitis (EAE), a mouse model for MS
Remyelination

I. Recruitment phase
(Proliferation, Migration)

Acute lesion

Recruitment of OPCs

Oligodendrocyte progenitor cells (OPCs)

Franklin NatRevNeurosci 2002
Microglia
the macrophages of the brain
Microglia

Wenbiao Gan (NYU)
Neurodegeneration

Healthy brain

With advanced Alzheimer

Alzheimer plaques
iPS cells

Motor neurons from patient with ALS

John B. Gurdon, Shinya Yamanaka
2012 Physiology and Medicine Nobel Prize

Dimos/Eggn Lab at HSCI.
Gensat project
http://www.gensat.org/index.html

NIH funded, publicly available gene expression atlas of the developing and adult nervous system

different shapes and differential gene expression