Axon Pathfinding is a Complex Problem!

Fig. 5.1
What is required of growth cones?

• Sensory ability
  – recognize static/dynamic molecular cues
    • intermediate targets
    • final destinations
  – recognize secreted molecules as local cues
    • gradients
    • concentration dependence
  – modulate responses to cues based on spatial and temporal factors
• Motor ability (through actin and microtubules)
  – Growing (trophic response)
  – Turning (tropism)
    • Attraction
    • Repulsion
  – Stopping
• Autonomy
  – Partial independence from soma

Growth Cones
Ramon y Cajal’s “battering rams”

Fig. 5.11
Growth cones are autonomous

Pioneer axons, stepping stones, and guidepost cells facilitate pathfinding
Evidence for guidance by local cues

Salamander hindbrain Mauthner neurons

Growth Cone Behavior

Shapes vary depending on task

http://www.pdn.cam.ac.uk/staff/holt/small.mov
Growth Cones
Ramon y Cajal’s “battering rams”

Fig. 5.10, 12

Central domain  Actin filaments  Microtubules  Merge

Growth Cone Structure

Fig. 5.10, 12
Axon Growth Mechanism

Actin movement is similar to tank treads. Actin monomers are added at the tips and removed at the base of the F-actin filament.

Growth is inversely related to the rate of retrograde F-actin flow.

Stasis: retrograde flow matches monomer addition.

Myosin inhibition slows retrograde flow and promotes filopodial elongation.

Role of actin in axon guidance

Actin is necessary for guidance.

Control

Myosin inhibition

http://www.youtube.com/watch?v=4P3gj2SHLOw

http://www.youtube.com/watch?v=iBh9wG8W17s&feature=related

Fig. 5.13-14
The Cytoskeleton Steers Growth Cones

http://www.youtube.com/watch?v=3R9SOtcSEuA&feature=endscreen

Fig. 5.15-16

Clutch Hypothesis

Nature Reviews | Molecular Cell Biology
Growth cones are highly dynamic

Ena/Vasp is anti-capping agent and allows actin filaments to continue elongating

Inhibit Ena/Vasp


Dendrite vs. Axon Formation

Red: microtubules
Green: Actin
Dendrites: MAP2
Axons: Tau, Gap-43
Mechanical Guidance

Fig. 5.20

Adhesion Mechanisms

Fig. 5.21

Fig. 5.22
Adhesion Molecules

Directional Information

Fig. 5.23

Fig. 5.25
Exam 2 material is everything previous to this slide

Experimental Approaches to the Labeled Pathways Hypothesis

Note panels C-F missing!
Regulation of Adhesion by Polysialic Acid

PSA mnemonic - pretty slippery axons
Endo-neuraminidase strips the PSAs

Response of axons to CAMS can change over time/space

Fig. 5.28

Fig. 5.30
Repulsive Guidance

Growth cone collapse

Fig. 5.31, 32

Chemotaxis: Long distance guidance

Fig. 5.34
Targets release chemotropic agents

Fig. 5.35

Netrin Gradients and Commissural Guidance

Fig. 5.36
Local Guidance vs. Diffusible Attractants?

Fig. 5.37

Midline Crossing

Fly

Chick

Slit (blue) expressed at midline, Robo (Slit’s receptor) on growth cones. Slit is repulsive.

Comm is expressed on commissural axons and downregulates Robo to allow crossing

Robo binds Slit to prevent midline crossing in axons that don’t express Comm

Fig. 5.38

Fig. 5.39

Fig. 5.41
Midline Crossing: Chick & Fly
Neutralizing repellants

Robo3A = Rig1, acts like comm and sequesters Robo1 to promote crossing.

Repulsion vs. Attraction by Netrin: Netrin (unc-6);
unc-40 = attractive netrin receptor = Dcc/frazzled;
unc-5 = repulsive netrin receptor.

Repulsion vs. Attraction by Netrin:
Attraction
Repulsion
Mediated by cAMP or cGMP interactions with the cytoskeleton
Optic Nerve Pathfinding

Fig. 5.45

Fig. 5.44

Attract Repel
From LeTourneau

Microtubules

Fig. 5.17