

Lecture 35 – Development I – Jessell

I. Guidance of Axon Outgrowth

A. Growth cone

1. senses and responds to environmental cues, thereby guiding axon growth
2. specialized structure
 - a. microtubules in central region
 - b. actin filaments
 - i. in peripheral region, extending out into digitate filopodia
 - ii. continually undergoing polymerization, which drives extension, and depolymerization
 - c. membrane cycle contributes to growth, with exocytosis to add surface membrane in periphery and endocytosis centrally

B. Guidance cues

Growth is controlled by multiple cues, both positive and negative.

1. extracellular matrix cues that are permissive for growth
 - a. laminins, collagens, etc. which bind to heterodimeric receptors (integrins)
 - b. binding of matrix protein to integrin can, through internal adapter proteins, cause matrix to become linked to internal actin cytoskeleton
2. cell surface cues that promote fasciculation
 - a. fasciculation allows axons to grow along scaffold laid down by pioneer axons
 - b. certain members of immunoglobulin superfamily, such as NCAM, mediate Ca^{++} -independent binding; NCAM binding is homophilic
 - c. cadherins mediate Ca^{++} -dependent binding
3. cell surface cues that inhibit growth
 - a. cause collapse of growth cone
 - b. semaphorins (collapsins) bind to neuropilin and plexin receptors
 - c. some semaphorins are secreted
4. chemoattraction
 - a. diffusible cue is released from distant source, establishing an attractive gradient
 - b. netrin 1 released from ventral floor plate attracts commissural axons to midline
 - c. netrins bind to receptor containing DCC and unc-5H subunits
5. chemorepulsion
 - a. diffusible cue released from distant source, establishing a repulsive gradient
 - b. netrin is chemorepellent if activity of cAMP-dependent protein kinase (PKA) is blocked within growth cone

II. Topographic projection onto target

A. Retina onto optic tectum (lower equivalent of superior colliculus)

1. axons from neurons in anterior retina synapse on neurons in posterior tectum, with neurons from progressively more posterior regions of retina projecting to progressively more anterior regions of tectum
2. similar dorso-ventral gradient, with dorsal retina projecting to ventral tectum
3. *in vitro* assay shows that axons from posterior retinal neurons avoid posterior tectal membranes, while growing well on anterior tectal membranes

4. ephrins distributed in gradients on tectum help create topographic projection by binding to eph kinases on ingrowing retinal axons

III. Target influence on neuronal survival

Many neurons die during normal development. Survival is regulated by target cells.

Neurotrophic hypothesis: The target releases a trophic factor which promotes the survival of its innervating cells. However, this factor is released in amounts insufficient for the survival of all of the neurons, so there is competition for factor among the innervating axons. Those cells that take up insufficient trophic factor die.

A. Classes of trophic factors

1. neurotrophins

a. e.g. NGF

b. bind to specific trk tyrosine kinase receptors

c. survival factors for primary sensory neurons, with different subtypes of neuron expressing different trk receptors and, therefore, using different neurotrophins

2. cytokines

a. e.g. CNTF

3. GDNF family

B. Mechanism of action

1. Suppress intrinsic cell death program, where caspase is activated by ced-4 family protein (Apaf 1 in vertebrates). Trophic factor causes activation of Bcl-2 family protein which suppresses ced-4 family protein.

2. Binding of trophic factor initiates multiple signal transduction pathways to mediate multiple functions, one of which is cell survival.

Relevant reading: chapters 53 and 54 in “Principles”