Current Model for how cells become neural

1) Default state is neural
2) Local secretion of BMPs by epidermis inhibits neural fate
3) Local secretion of noggin, chordin by dorsal lip or mesoderm inhibits BMP signaling
4) Inhibition of BMP signaling give rise to neural fate

Double Inhibition Model for Neural fate

Neural Development

How do cells become neurons?

– Environmental factors
  • Inductive events
– Genetic factors
  • Competence
    Cell lineage
    Timing

- How do ectodermal cells become neural cells?

- How is polarity established?
  Dorsal Ventral
Neurulation: Formation of the Neural Tube

Looking at Dorso Ventral Patterning

During development, various structures are formed as the posterior part of the neural tube becomes the spinal cord:

**Dorsal**
- Roof Plate
- Dorsal Root Ganglion
- Sensory Neurons

**Ventral**
- Floor Plate
- Motor Neurons

Patterning of the spinal cord is induced by notochord

Experiment: Graft an extra notochord near neural tube

Result: An extra floor plate forms
Induction by floor plate

Experiment: Graft an extra floor plate near the neural tube

- extra lateral floor plate = ectopic lateral floor plate
- extra dorsal floor plate = ectopic floor plate where roof plate should be

Result: An extra floor plate forms

Extra floor plates = extra motor neurons

Motor neurons always form at a set distance from the source of inducing signal.

Induction of dorsal/ventral neural tube formation

Determination of cell-fates in the spinal cord

But what are the inducers?
Looking at Dorso Ventral Patterning

What is the signal released by the notochord?

Sonic Hedgehog (SHH) is a secreted protein expressed in the floor plate and notochord and it is the signal that induces the ventral fate.

Properties of Sonic Hedgehog

1. Secreted molecule
2. Modification by cholesterol keeps most SHH on cell-surface
3. Receptor for SHH is Patched, activates a signaling cascade, leading to changes in gene expression

Patterning in the Spinal Cord—many different cell-fates

Loss of SHH leads to loss of ventral cell-fates
Addition of SHH produces ventral cell-fates

How does one molecule induce multiple fates?
Patterning in the Spinal Cord—Expression of Different transcription factors

The particular fate of different cells depends on the amount of SHH that they are exposed to.

- Low SHH → Ventral Interneurons
- Medium SHH → Motor Neurons
- High SHH → Floor Plate Cells

Model: Different SHH concentrations induce different cell fates

Morphogen hypothesis

1. Morphogens are secreted molecules that diffuse from a point source.
2. A morphogen determines cell fate based on its concentration.
3. Morphogens control the expression of downstream genes.
4. Different concentrations of a morphogen may turn on/off the expression of different target genes.
How a gradient produces different cell-types

Is SHH a morphogen?
1. Concentration dependence of cell-fates
2. Direct action at a distance
Different concentrations of SHH produce different cell fates
Expt: add different SHH concentrations to young spinal cord explants
Result: different genes are expressed in a dose-dependent manner

SHH acts directly on cells over a distance
Expt: Locally add dominant-negative SHH receptor to spinal cord to decrease SHH signaling
Result: Less SHH causes cells to take on a more dorsal fate

How does a graded concentration give sharp boundaries of gene expression?
Two mechanisms that generate sharp boundaries:

1. Cell A adheres to Cell A (or Cell A repels Cell B)
2. Cell A inhibits Cell B fate and Cell B inhibits Cell A fate

The vertebrate spinal cord and the Drosophila embryo use gradients to induce different cell fates

Bicoid is a morphogen that sets up the body plan
Nobel 1995: Lewis, Nusslein-Volhard, Wieschaus
Genetic basis of embryonic development

The other half of the story: BMPs regulate dorsal fates

SHH is not the only inducer of the neural tube
Expt: ablate the notochord
Result: no ventral motor neurons, expansion of dorsal sensory neurons
The roofplate induces the dorsal cell fate

Expt: Ablate the roofplate, look at which genes are expressed

Result: loss of dorsal fates, expansion of ventral fates

BMP4 is produced by the roof plate. It induces dorsal cell fates and inhibits ventral fates.

What key experiments would show this?

Looking at Dorso Ventral Patterning

• SHH signaling is required to adopt a ventral fate
• BMP is necessary to induce dorsal cell fates
• BMP inhibits ventral fate
• SHH inhibits dorsal fate
Practical Implications: Manipulation of Cell fates

The pathway to induce a motor neuron is simple

Differentiation of embryonic stem cells into motor neurons

Expt: treat ES cells with SHH, look for expression of motorneuron genes, transplant motorneurons into the developing mouse embryo

Result: motorneurons made in a dish function as motorneurons in a mouse

Therapy for degenerative disorders?

Cell fate determined by position in a gradient!!!!!!