Neural induction: classic experiment Spemann organizer

Neural induction: classic experiments
BMP signaling is important in neural induction.

Endogenous BMP inhibitors are neural inducers: noggin.
BMP inhibitors are expressed in the organizer.

Noggin/chordin double ko

A-P patterning: Induction of the nervous system by mesoderm is region-specific.

Or...
Step 2: Posteriorization

What are the posteriorizing signals?

Dkk1 over-expression induces an extra head

Dkk1 knockout mouse has a severe loss of head structures

Figure 2.10 – Source: Development of the Nervous System

Travis Science – Linecome, Inc. – 08/2013 – lr
Retinoic acid is important for patterning the nervous system.
Step 2: Posteriorization
What are the posteriorizing signals?

Retinoic Acid is an unusual developmental signaling molecule

Evidence for the posteriorizing effect of Retinoic Acid

1) Raldh1a2 is expressed in the ventrolateral mesendoderm
2) Loss of RA causes the loss of posterior identities
Evidence for the posteriorizing effect of Retinoic Acid

3) Excess RA posteriorizes the CNS

4) Knock-down of an RA antagonist posteriorizes the CNS

The Nervous System Starts Out as a Flat Epithelium

The Notochord is an Inducer of Ventral Neural Fates
Sonic Hedgehog (shh) Expression

Hedgehog signaling greatly simplified
Hedgehog signaling greatly simplified  

**No Shh**

- **Ptchd1**
- **Smo**
- **GliA**
- **GliR**

**Class I genes**

**Class II genes**

---

Hedgehog signaling greatly simplified  

**Shh**

- **Shh**
- **Ptchd1**
- **Smo**
- **GliA**
- **GliR**

**Class I genes**

**Class II genes**

---

Gli transcription factors in Shh signaling

- **Gli2** is an activator and is degraded without Shh.
- **Gli3** is proteolytically processed into a repressor without Shh, but with Shh turns into an activator.
- **Gli1** (also an activator) is regulated by Gli2/3, and so is upregulated by Shh signaling.
- Together the Gli proteins become activators with Shh.
Dorsal ventral patterning with Shh

Shh is released from the notochord and floorplate and diffuses dorsally

Shh from notochord and floorplate activates Gli in a ventral-dorsal gradient
Activation of target genes is Shh concentration dependent.

There is a transient olig2 response. Do cells first express olig2 and then Nkx2.2?
If Nkx2.2 cells go through an Olig2 expressing phase, they will be labeled with the Olig2-cre.

**b**

**Olig2**

**ROSA26-geo-STOP-geo-lacZ**

Shh activates a cross-repressing network of transcription factors.
Evolutionary Considerations

Patterning factors summary

<table>
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<th>Diagram Details</th>
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<td>Otx2, HH4, Gbx2, HH10</td>
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Some take-home messages

• BMP antagonists are the neural inducers
• Wnt, FGF and RA are the primary anterior-posterior patterning factors
• Shh/Bmp pattern the dorsal ventral axis
• Gradients of signals are translated to domains of differential gene expression
• Many of the factors that pattern the nervous system are derived from extra-neural sources