Neuroinduction

Diffusible morphogen

Endoderm and Mesoderm Involute with Gastrulation: Induction of the Neural Plate from Neuroectoderm, by the Underlying, Closely Apposed Mesoderm.
Hilde Mangold and Hans Spemann

- Key experiments performed in 1924 at the University of Freiburg, Germany.
- Hilde Mangold was a 26 year old graduate student. She died tragically in an accidental heater explosion.
- Hans Spemann was awarded the Nobel Prize in 1935.

Hilde Mangold and Hans Spemann Experiments (1924).

A) Mangold-Spemann Organizer

B) The “organizer” is sufficient to induce a second nervous system.
Explant Experiments with Animal Caps from Amphibian Blastula.

Isolating Inducing Factors that Promote Neuronal Differentiation.
Models for Neural Induction

Model 1:

- Presumptive Neuroectoderm
- + "Epidermal factor"
- Epidermis
- + "Neuronal factor"
- Neurons

Model 2:

- Presumptive Neuroectoderm
- Epidermis ("default")
- + "Neuronal factor"
- Neurons

Model 3:

- Presumptive Neuroectoderm
- + "Epidermal factor"
- Epidermis ("default")
- Neurons

TGF-β Proteins Signal Through Heterodimeric Receptors and Smad Transcription Factors.

- TGF-β
- (activin)
- Receptor (type I + type II)
- Kinases (?)
- Transcription Factor (Smad)
- Gene Activation
A Dominant-Negative Receptor Subunit Blocks Activation of the Signaling Pathway.

Dominant-Negative (i.e. poison) Type II Receptor Subunit

Blocking TGF-β Signaling by Expression of a Dominant-Negative Receptor Causes Isolated Neuroectoderm to Become Neuronal.

Epidermal Cells

TGF-β Signaling is required to promote epidermal fate and inhibit neuronal fate.
BMP-4 / TGF-β Signaling Results in "Neural Epidermal Induction".

Models for Neural Induction

Model 1:

Presumptive Neuroectoderm

+ "Epidermal factor"

Epidermis

"Neuronal factor"

Neurons

Model 2:

Presumptive Neuroectoderm

Epidermis ("default")

+ "Neuronal factor"

Neurons

Model 3:

Presumptive Neuroectoderm

(+BMP-4)

+ "Epidermal factor"

Epidermis

(-BMP-4)

Neurons ("default")

TGF-β: Transforming Growth Factor - β
BMP-4: Bone Morphogenic Protein - 4
BMP-4 (Secreted by Neuroectodermal Cells) Inhibits Neuronal Fate and Promotes Epidermal Fate.

Dissociation dilutes BMP-4 activity.

Recombinant BMP-4 promotes epidermal fate and inhibits neuronal fate.

BMP-4 mRNA is expressed in presumptive ectoderm.

(Fainsod, et al., 1995)
Are there native antagonists of BMP-4?
Secreted from underlying mesoderm?
Yes... chordin / noggin / follistatin.

Chordin expresses in mesoderm

(Sasa, et al., 1995)

Noggin cRNA injections rescue ventralized embryos.

+ Noggin injection

(Smith and Harland, 1992)
Differential Subtractive Screen Yields Chordin, a BMP-4 antagonist. (1994)

P³²⁻Labelled cDNA Probes

Functional Expression Cloning Yields noggin, a BMP-4 antagonist. (1992)
Chordin / noggin / follistatin antagonize BMP-4 activity by directly binding and inactivating BMP-4.

(Zimmerman, Jesus-Escoba and Harland, 1996)

Crystal Structure of Noggin-BMP Complex Confirms Biochemical and Functional Studies

(Groppe, et al., 2002)
Molecular Mechanism of Neuralization.

Neuroectoderm induced to become neuronal by suppression of BMP-4, which inhibits the default neuronal fate.

TGF-β Proteins Signal Through Heterodimeric Receptors and Smad Transcription Factors.
The Mechanism for Neural Induction is Evolutionarily Conserved between Vertebrates and Invertebrates.

<table>
<thead>
<tr>
<th>Vertebrates</th>
<th>Drosophila</th>
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</thead>
<tbody>
<tr>
<td><strong>Ligand</strong></td>
<td>BMP-4</td>
</tr>
<tr>
<td><strong>Receptor</strong></td>
<td>Type I: punt</td>
</tr>
<tr>
<td><strong>Antagonist</strong></td>
<td>noggin</td>
</tr>
<tr>
<td><strong>Transcription Factor</strong></td>
<td>Smad1</td>
</tr>
<tr>
<td></td>
<td>Smad2</td>
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<td></td>
<td>Smad4</td>
</tr>
</tbody>
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BMP-4 is a member of the large evolutionarily conserved TGF-β gene family, which mediates many tissue inductive events.

![Diagram showing relationships between members of the TGF-β superfamily](image-url)

Figure 17.5 Relationships between members of the TGF-β superfamily. (After Hogan, 1996.)
**Neurogenesis: Inductive Mechanisms.**

1. Neuroectodermal cells choose either a neuronal or epidermal cell fate.

2. Interactions between mesoderm and neuroectoderm induce neuroectoderm to adopt the neural fate.

3. Induction acts through signaling by a secreted protein, Bone Morphogenic Protein-4 (BMP-4), made by neuroectodermal cells.

4. BMP-4 inhibits neuralization and promotes the epidermal fate in neighboring cells.

5. Mesodermal cells secrete proteins (Chordin, Noggin, Follistatin) which directly bind and antagonizes BMP-4 activity.

6. Neuroectodermal cells become neurons by suppression of BMP-4 activity by secreted proteins from underlying mesodermal cells.

7. The “default” state of neuroectodermal cells is neuronal.

8. This inductive mechanism is conserved between vertebrates and invertebrates.

9. BMP-4 is a member of the Transforming Growth Factor (TGF-β) family of signaling molecules. Similar signaling events maybe locally re-employed later in the developing nervous system.