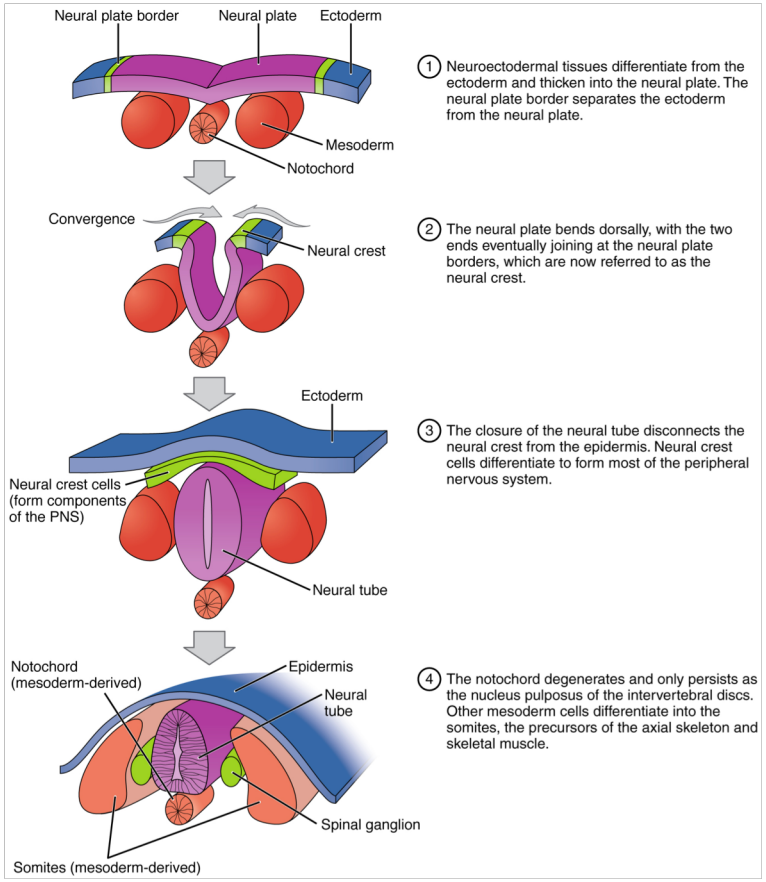
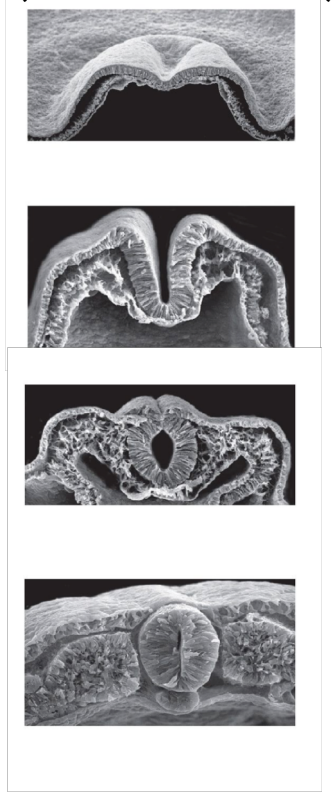
Neural Induction

Nervous system development in Vertebrates

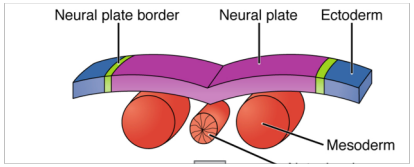
- The **ectoderm** gives rise to the columnar epithelium of the **neural plate** (the precursor of the CNS)
- The **neural crest cells** originate at the dorsalmost region of the neural tube →PNS + many different cell types…
- Ectodermal cells at the most anterior edge of the neural–epidermal boundary give rise to **placodes** that will form sensory organs as well as **cranial sensory ganglia**

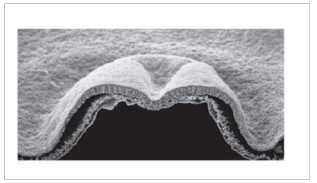


EM
(chick neural tube)



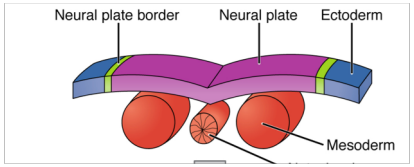
Neural Induction

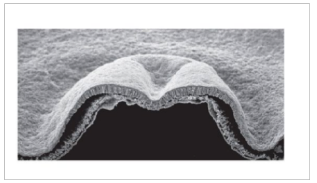




When and **How** embryonic tissue becomes **committed to the neural fate**?

Neural Induction





When

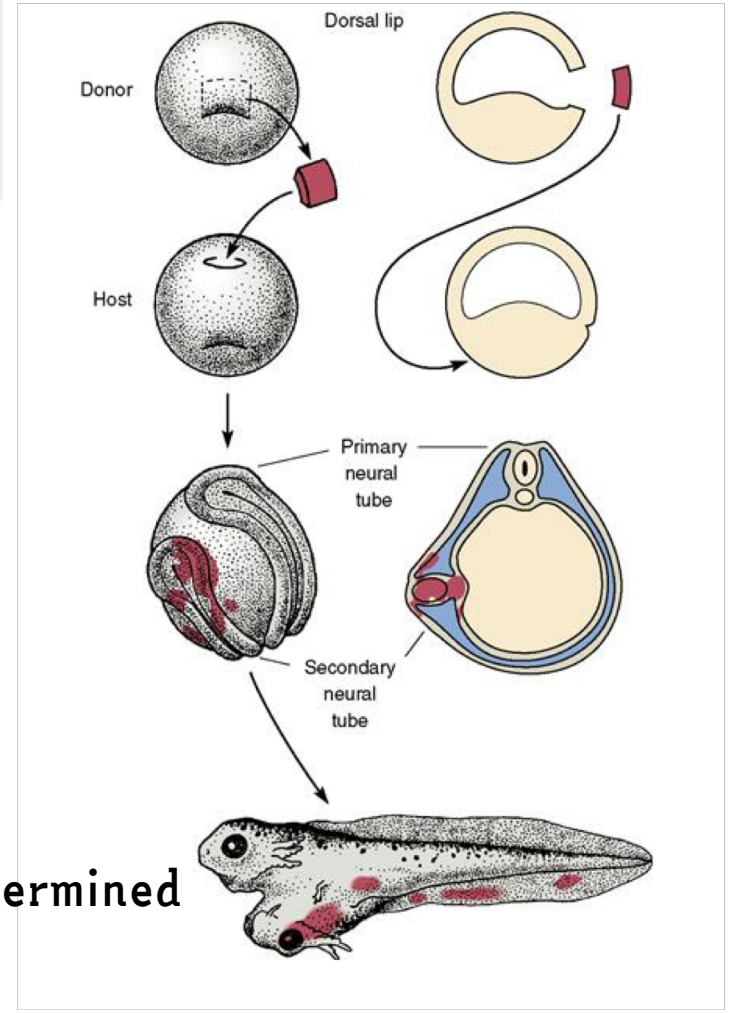
At the gastrula stage (or earlier?)

How

Signals from a cluster of cells (the organizer)
trigger neural development
in the dorsal ectoderm

The first demonstration:
Spemann and Mangold experiment (1924)

- Newt embryos (*white Triturus cristatus and the dark T. taeniatus or T. alpestris*)
- Gastrulation stage
- Transplantation of the dorsal lip of the blastopore (**The Spemann organizer**)

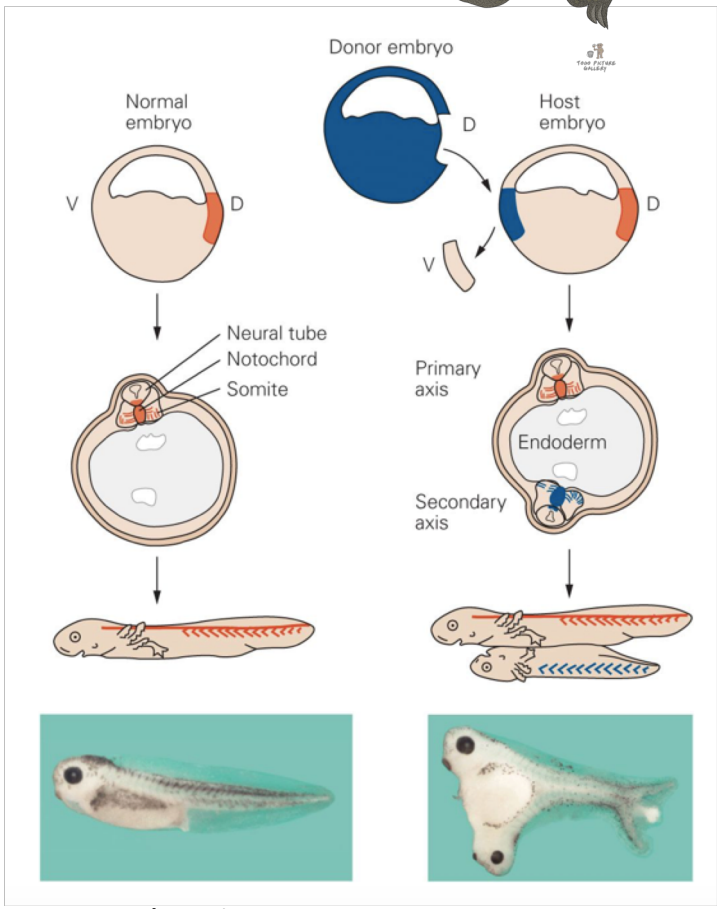


First demonstration that cell and tissue fate can be determined by signals received from other cells

Nobel Prize to Hans Spemann (1935)

X. laevis embryos

video



E. De Robertis

Transplanted organizer cells:

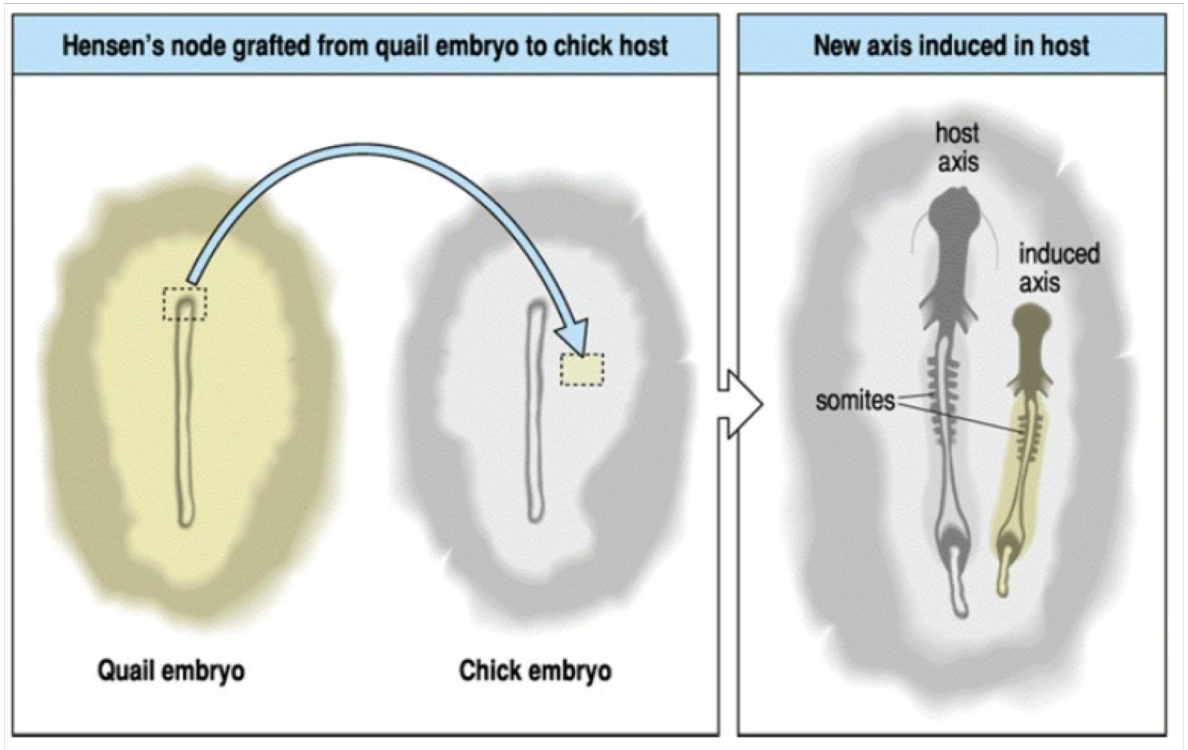
- Follow their own developmental program (midline mesoderm tissue: notochord and somites)
- Induce host cells to change their fate forming a second embryonic axis
  → neuralization
  → dorsalization

cells can adopt their developmental fate according to their position when instructed by other cells

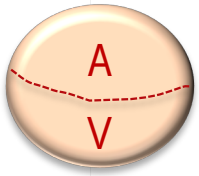
start@unito

Evolutionary conservation of the organizer

Transplantation experiments reproduced in fish, chick and mouse embryos...



The Animal Cap Explant Assay



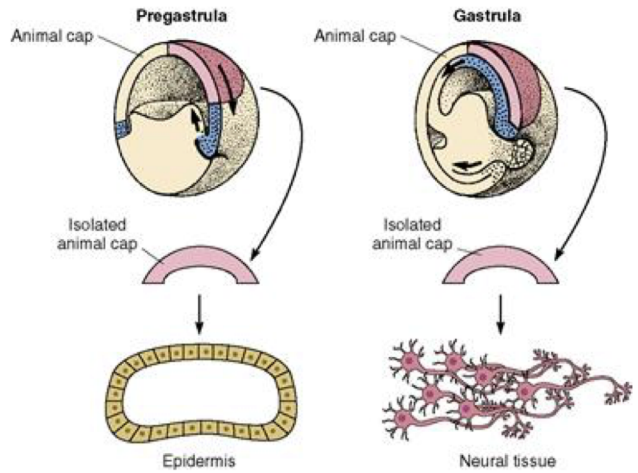


Fig. 1.11 Isolation of fragments of embryos at different stages of development demonstrates when tissue becomes committed to the neural lineage. If the animal cap is isolated from the rest of the embryo (left), the cells develop as epidermis, or skin. If the same region of the embryo is isolated a few hours later, during gastrulation (right), it will develop into neural tissue (shown in the figure as red neurons). Experiments like these led to the idea that the neural lineage arises during gastrulation.

Experimental approach: isolation and culture of tissue fragments of the animal pole at different stages of development (Amphibian embryos)

Results: cell types differentiate depending on the stage and co-culture tissue

1° Hypothesis on Neural Induction:

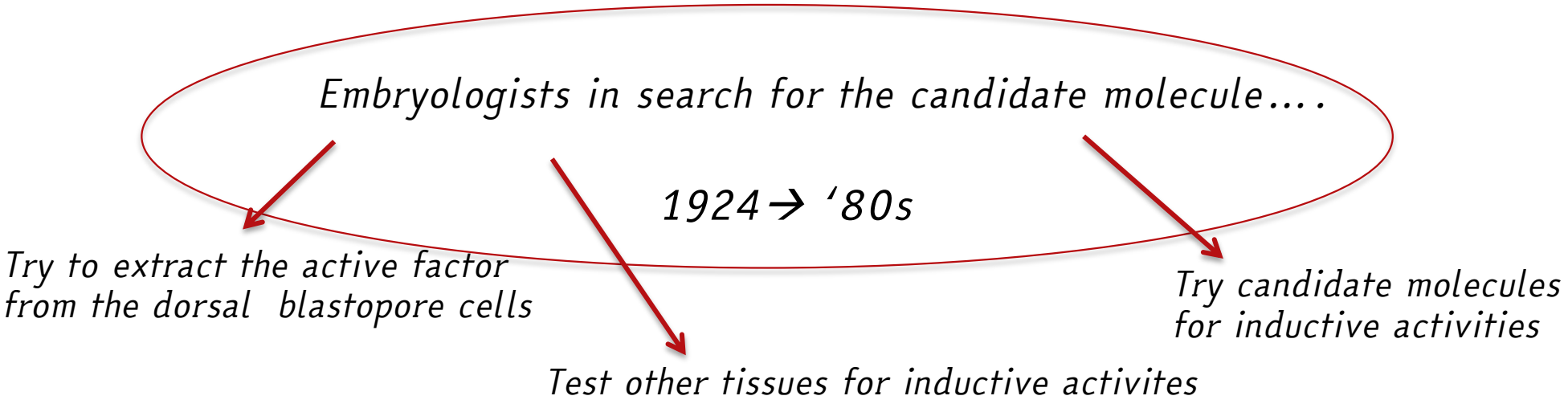
- the ectoderm forms epidermis as a default state
- the organizer and resulting notochord, through secreted soluble molecules, instruct the ectoderm to form neural tissue

→ What is the molecular nature of the **neural inducer?**

1° Hypothesis on Neural Induction:

- the ectoderm forms epidermis as a default state
- the organizer and resulting notochord, through secreted soluble molecules, instruct the ectoderm to form neural tissue

→ What is the molecular nature of the **neural inducer?**



1° Hypothesis on Neural Induction:

- the ectoderm forms epidermis as a default state
- the organizer and resulting notochord, through secreted soluble molecules, instruct the ectoderm to form neural tissue

→ What is the molecular nature of the **neural inducer?**

Embryologists in search for the candidate molecule….

1924→ '80s

BUT …the animal cap had the capacity to non-specifically convert to neural fate in response to a variety of materials …

Cell Differ Dev. 1989 Dec;28(3):211-7.

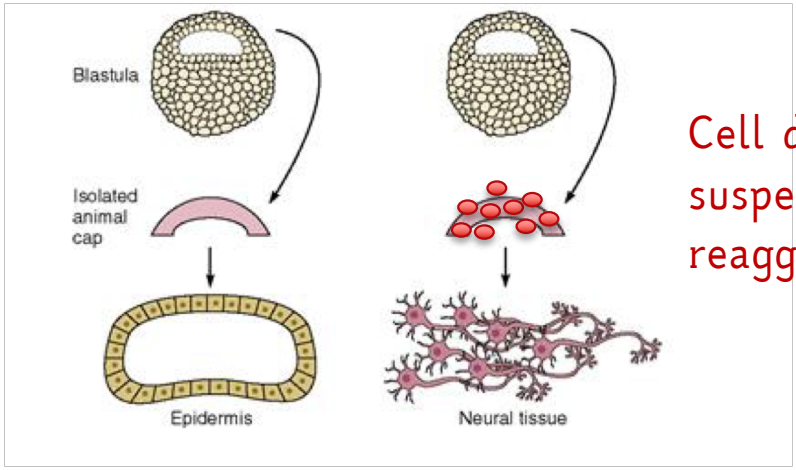
Neural differentiation of Xenopus laevis ectoderm takes place after disaggregation and delayed reaggregation without inducer.

Grunz H[1], Tacke L.

⊕ Author information

Abstract

When Xenopus blastula or early gastrula ectoderm is disaggregated and cells are kept dispersed for up to 5 h prior to reaggregation, the resulting spheres will differentiate into large neural structures. In contrast, dissociated and immediately reaggregated ectoderm will only differentiate into ciliated epidermis (so-called 'atypical epidermis'). Ectoderm treated with mesoderm-inducing XTC-conditioned medium during the period of reaggregation immediately after disaggregation will only form one- or two-cell types (notochord and somites) only. Ectoderm treated with XTC-factor prior to disaggregation will differentiate into a large variety of cell types.



Cell dissociated and maintained in suspension (1-5 hrs) before reaggregation → **neural tissue**

? ? ? ?

start@unito

Cell Differ Dev. 1989 Dec;28(3):211-7.

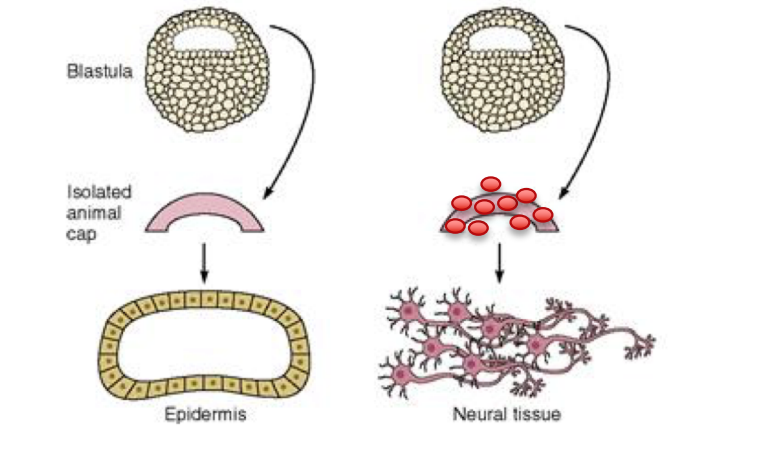
Neural differentiation of Xenopus laevis ectoderm takes place after disaggregation and delayed reaggregation without inducer.

Grunz H[1], Tacke L.

⊕ **Author information**

Abstract

When Xenopus blastula or early gastrula ectoderm is disaggregated and cells are kept dispersed for up to 5 h prior to reaggregation, the resulting spheres will differentiate into large neural structures. In contrast, dissociated and immediately reaggregated ectoderm will only differentiate into ciliated epidermis (so-called 'atypical epidermis'). Ectoderm treated with mesoderm-inducing XTC-conditioned medium during the period of reaggregation immediately after disaggregation will only form one- or two-cell types (notochord and somites) only. Ectoderm treated with XTC-factor prior to disaggregation will differentiate into a large variety of cell types.



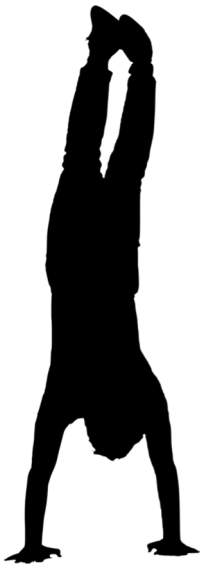
Neural fate can be derived from competent ectoderm in the absence of signals from the organizers

The **absence**, not the presence, of an intercellular signal is necessary for neural differentiation

The default model

The **default fate** of ectodermal cells is **neural differentiation**

This fate is prevented by signals from neighboring cells



The inducer is a de-repressor of neural fate

→ What signals repress neural differentiation?

→ What does organizer tissue provide to overcome the effects of the repressor?

The need to distinguish direct versus indirect Neural Induction

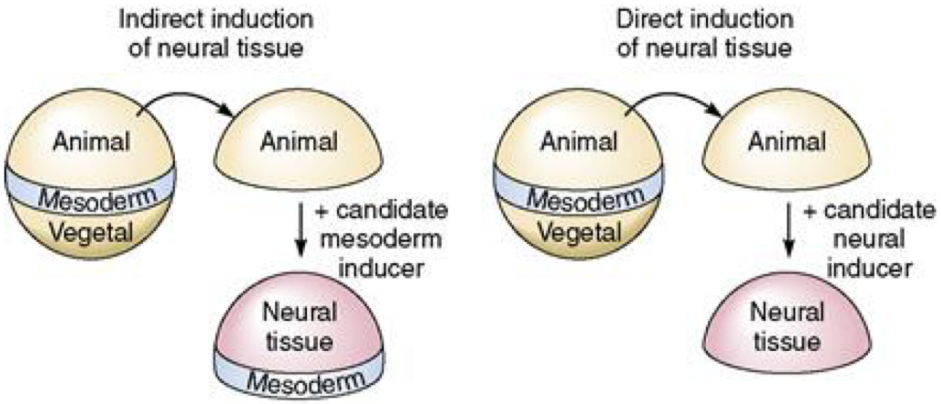
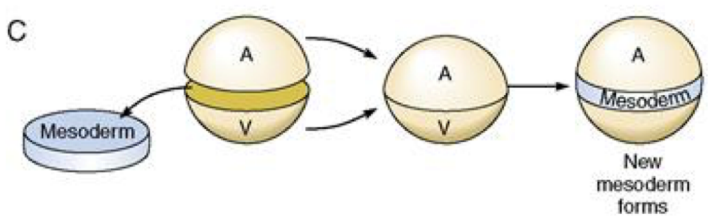
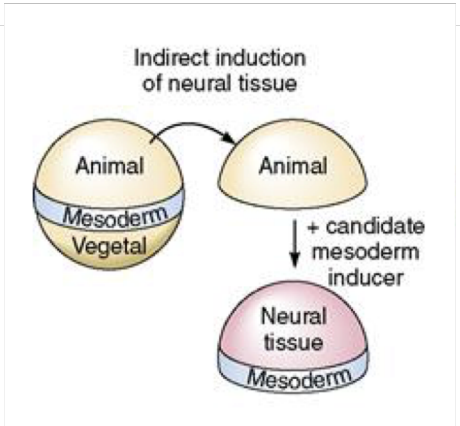


Fig. 1.14 Indirect neural induction versus direct neural induction. The organizer transplant experiments show that the involuting mesoderm has the capacity to induce neural tissue in the cells of the animal cap ectoderm. When assaying for the factor released from mesoderm that is responsible for this activity, it was important to distinguish between the direct and indirect

Activin





In the *Xenopus* blastula, the cells in the middle of the embryo become **mesodermal** by responding to **activin** (or an activin-like compound) produced in the vegetal hemisphere.

- At the blastula stage **activin** can promote formation of neural tissue
- At the gastrula stage **activin** is ineffective at promoting the formation of neural tissue

(the gastrula ectoderm loses competence to form mesoderm in response to activin)

Activin promotes formation of neural tissue through an indirect effect by the dorsal mesoderm (which is induced by activin)

Main criteria for an authentic neural inducer

- It should be able to induce neural tissue from animal cap ectoderm in the absence of dorsal mesoderm → **direct induction**
- Competent ectoderm should be responsive to the neural inducer at the gastrula stage (when dorsal mesoderm can still induce neural tissue)
- It must be present at the right **time** and **place** to account for normal neural development
- Elimination of its activity should block normal neural development

Mechanistic demonstrations

An authentic Neural Inducer should …

- …be at the right place at the right time → **LOCATION**
- …when signal is blocked – no response → **NECESSITY**
- ….be able induce the response peraphs ectopically → **SUFFICIENCY**

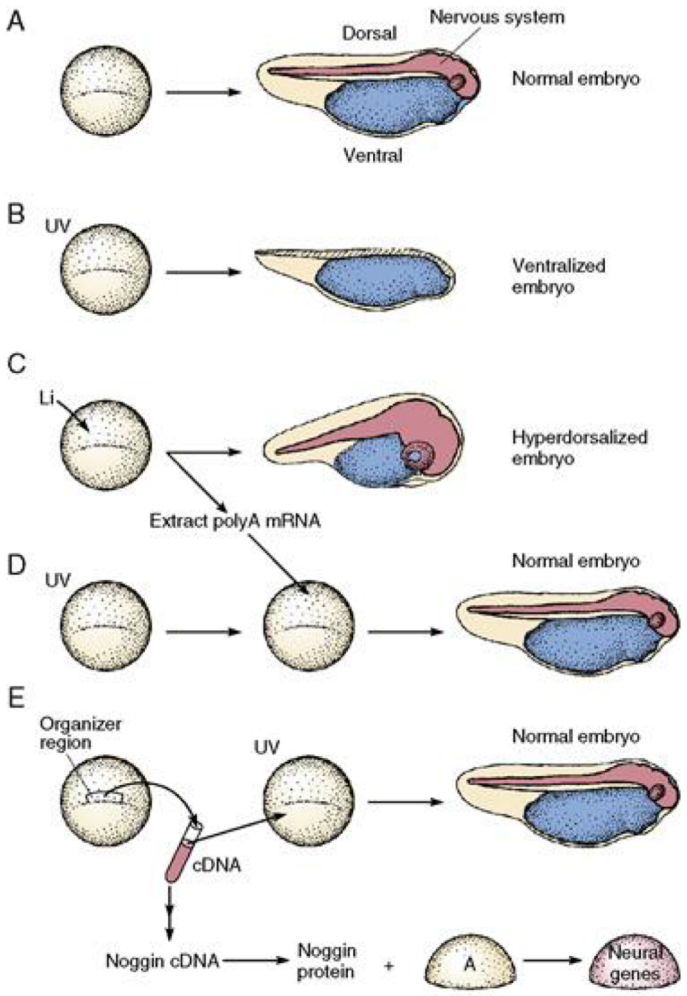
Science. 1993 Oct 29;262(5134):713-8.

RESEARCH ARTICLE

Neural Induction by the Secreted Polypeptide Noggin

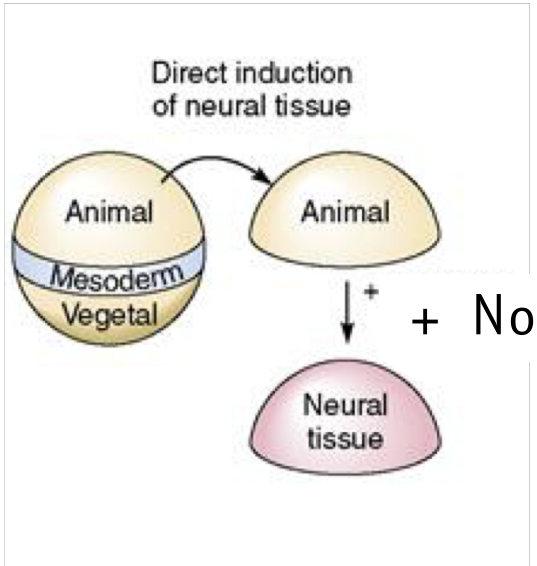
Teresa M. Lamb, Anne K. Knecht, William C. Smith, Scott E. Stachel, Aris N. Economides, Neil Stahl, George D. Yancopolous, Richard M. Harland*

The Spemann organizer induces neural tissue from dorsal ectoderm and dorsalizes lateral and ventral mesoderm in *Xenopus*. The secreted factor noggin, which is expressed in the organizer, can mimic the dorsalizing signal of the organizer. Data are presented showing that noggin directly induces neural tissue, that it induces neural tissue in the absence of dorsal mesoderm, and that it acts at the appropriate stage to be an endogenous neural inducing signal. Noggin induces cement glands and anterior brain markers, but not hindbrain or spinal cord markers. Thus, noggin has the expression pattern and activity expected of an endogenous neural inducer.



start@unito

Noggin added to blastula animal caps induces the expression of neural tissue specific genes (NCAM, XIF3, Beta-tubulin) in the absence of mesoderm



+ Noggin

Analysis of specific markers (neural and mesoderm)

NCAM
Beta-tubulin (isoform expressed in hindbrain and spinal cord)
XIF3 (neurally expressed intermediate filament gene)

Muscle actin
Goosecoid (early mesoderm marker)
Brachyury (Xbra) (early mesoderm marker)

Same results at the gastrula stage…

Cell. 1994 Dec 2;79(5):779-90.

Xenopus chordin: a novel dorsalizing factor activated by organizer-specific homeobox genes.

Sasai Y[1], Lu B, Steinbeisser H, Geissert D, Gont LK, De Robertis EM.

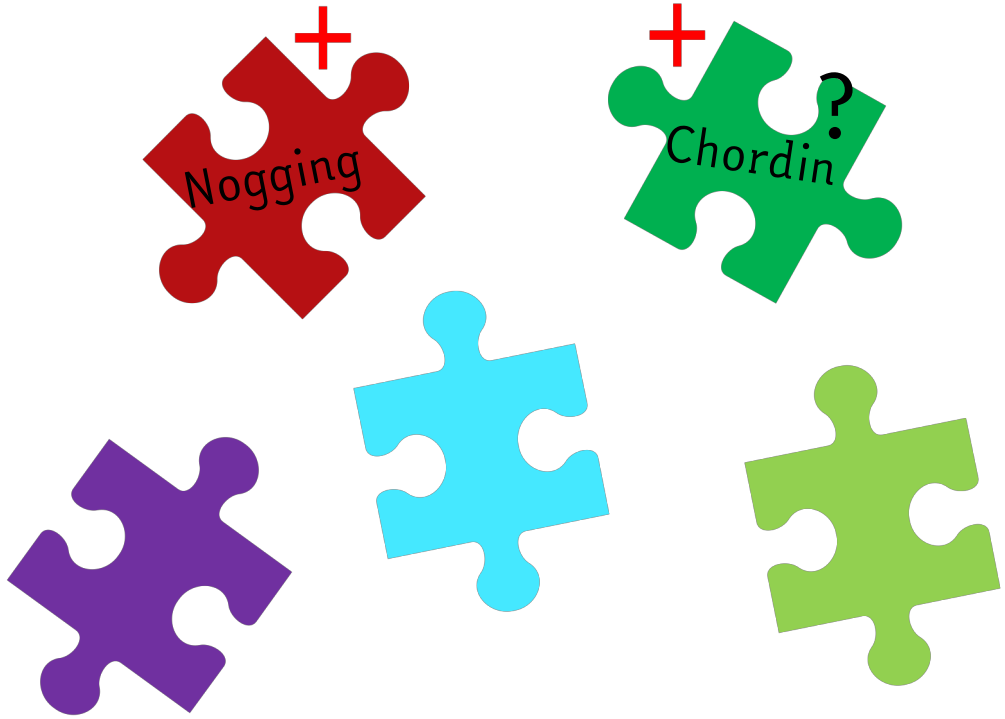
Author information

Abstract

A Xenopus gene whose expression can be activated by the organizer-specific homeobox genes goosecoid and Xnot2 was isolated by differential screening. The chordin gene encodes a novel protein of 941 amino acids that has a signal sequence and four Cys-rich domains. The expression of chordin starts in Spemann's organizer subsequent to that of goosecoid, and its induction by activin requires de novo protein synthesis. Microinjection of chordin mRNA induces twinned axes and can completely rescue axial development in ventralized embryos. This molecule is a potent dorsalizing factor that is expressed at the right time and in the right place to regulate cell-cell interactions in the organizing centers of head, trunk, and tail development.

PMID: 8001117 [PubMed - indexed for MEDLINE] PMCID: PMC3082463 Free PMC Article

At this point possible direct neural inducers identified...
still no clues on how they may work!!!



Cell. 1994 Apr 22;77(2):273-81.

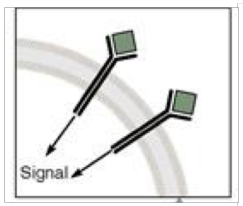
Inhibition of activin receptor signaling promotes neuralization in Xenopus.

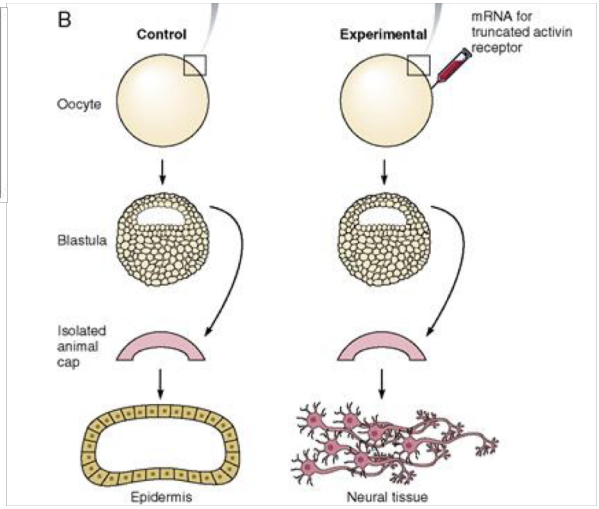
Hemmati-Brivanlou A[1], Melton DA.

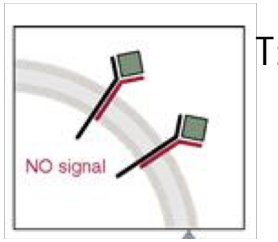
⊕ Author information

Abstract

Expression of a truncated activin type II receptor, which blocks signaling by activin, neuralizes explants of embryonic cells that would otherwise become epidermal cells. This neuralization is direct and does not require the presence of mesoderm. The induced neural tissue expresses general molecular markers of the central nervous system as well as an array of neural markers along the anteroposterior axis. In the context of the whole embryo, expression of this truncated activin receptor diverts prospective ectoderm and endoderm to a neural fate. We propose that inhibition of the activin type II receptor signaling causes the cells of Xenopus embryos to adopt a neural fate. These results, along with previous experiments performed in Drosophila, suggest that the formation of the nervous system in vertebrates and invertebrates occurs by a common strategy.







Truncated Activin type II receptor (dominant negative*) promotes neuralization

An activin-like molecule (TGF-β family) inhibitor of neuralization

*inhibits several TGFβ related factors

Neural Induction

Cell. 1994 Apr 22;77(2):283-95.

Follistatin, an antagonist of activin, is expressed in the Spemann organizer and displays direct neuralizing activity.

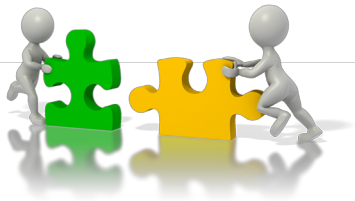
Hemmati-Brivanlou A[1], Kelly OG, Melton DA.

Author information

Abstract

In the accompanying paper, we show that the expression of a dominant negative activin receptor can convert prospective ectoderm into neural tissue, which suggests that activin is an inhibitor of neuralization. Here we report the isolation and characterization of an activin antagonist, follistatin, that can induce neural tissue directly in vivo. Follistatin RNA is localized in the Spemann organizer and notochord, tissues known to be potent neural inducers. We demonstrate that follistatin RNA and protein are able to block the activity of activin in embryonic explants. Furthermore, we show that follistatin RNA directly neuralizes ectodermal explants in the absence of detectable mesoderm. Thus, follistatin is present at the correct time and location to play a role in neural induction in vivo.

PMID: 8168135 [PubMed - indexed for MEDLINE]



Follistatin = Key regulator in adult reproductive system → by inhibition of Activin

start@unito

Nature. 1995 Jul 20;376(6537):249-53.

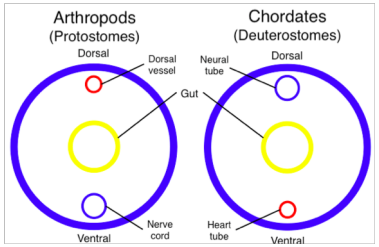
A conserved system for dorsal-ventral patterning in insects and vertebrates involving sog and chordin.

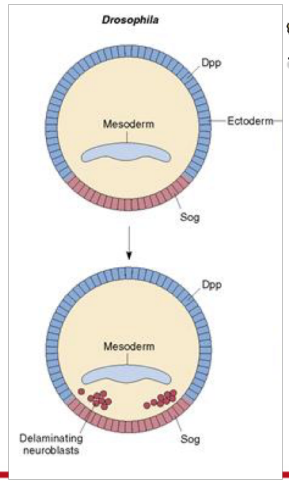
Holley SA[1], Jackson PD, Sasai Y, Lu B, De Robertis EM, Hoffmann FM, Ferguson EL.

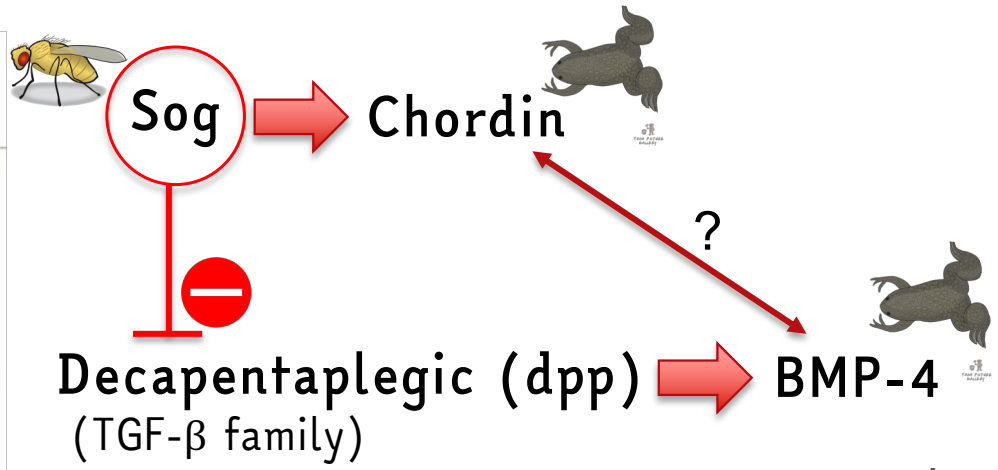
Author information

Abstract

Dorsal-ventral patterning within the ectoderm of the Drosophila embryo requires seven zygotic genes, including short gastrulation (sog). Here we demonstrate that sog, which is expressed in the ventrolateral region of the embryo that gives rise to the nerve cord, is functionally homologous to the chordin gene of Xenopus, which is expressed in the dorsal blastopore lip of the embryo and in dorsal mesoderm, in particular the notochord. We show by injections of messenger RNA that both sog and chordin can promote ventral development in Drosophila, and that sog, like chordin, can promote dorsal development in Xenopus. In Drosophila, sog antagonizes the dorsalizing effects of decapentaplegic (dpp), a member of the transforming growth factor-beta family. One of the dpp homologues in vertebrates, bmp-4, is expressed ventrally in Xenopus and promotes ventral development. We show that dpp can promote ventral fates in Xenopus, and that injection of sog mRNA counteracts the ventralizing effects of dpp. These results suggest the molecular conservation of dorsoventral patterning mechanisms during evolution.







Nature. 1995 Jul 27;376(6538):333-6.

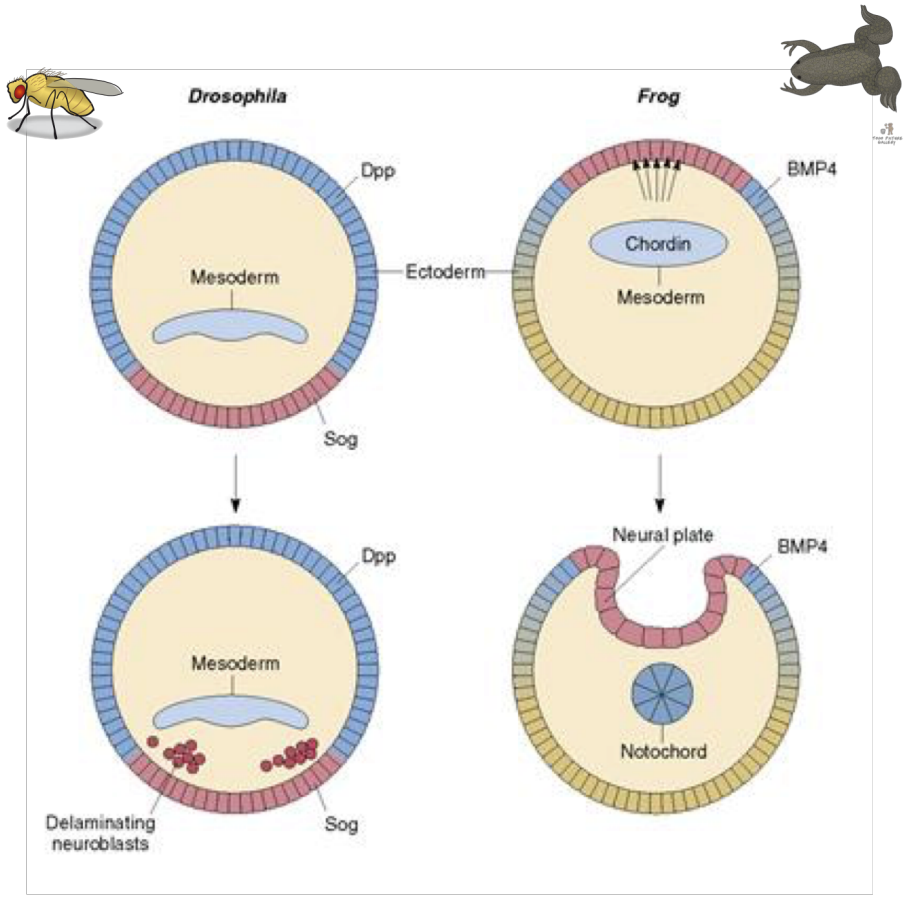
Regulation of neural induction by the Chd and Bmp-4 antagonistic patterning signals in Xenopus.

Sasai Y[1], Lu B, Steinbeisser H, De Robertis EM.

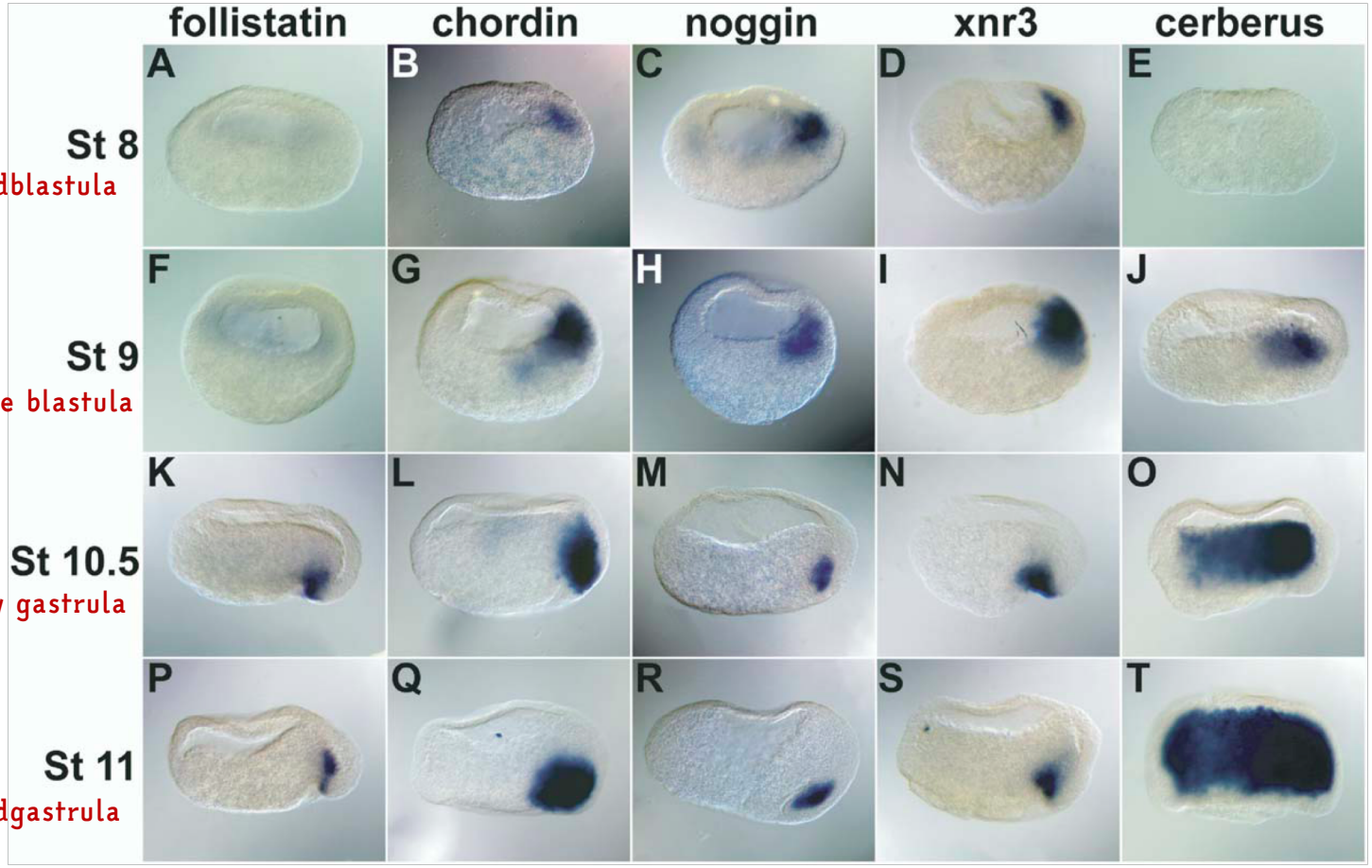
Abstract

In Drosophila the amount of neurogenic ectoderm, from which the central nervous system (CNS) derives, is regulated by a dorsal-ventral system of positional information in which two secreted molecules of antagonistic functions, decapentaplegic (dpp) and short-gastrulation (sog), play fundamental roles. The vertebrate homologue of dpp is either bmp-4 or bmp-2 (ref. 5), and the homologue os sog is chd (s-chordin). In Xenopus the CNS is induced by signals emanating from the organizer, and two proteins secreted by the organizer, noggin and follistatin, have been shown to induce neural tissue in animal-cap assays. Here we report that Chd, another organizer-specific secreted factor, has neuralizing activity and that this activity can be antagonized by Bmp-4. Inhibition of the function of the endogenous Bmp-4 present in the animal cap also leads to neural differentiation. We suggest that conserved molecular mechanisms involving chd/sog and bmp-4/dpp gene products pattern the ectoderm in Xenopus and in Drosophila.

Evolutionary conservation of molecular circuitry underlying Neural Induction

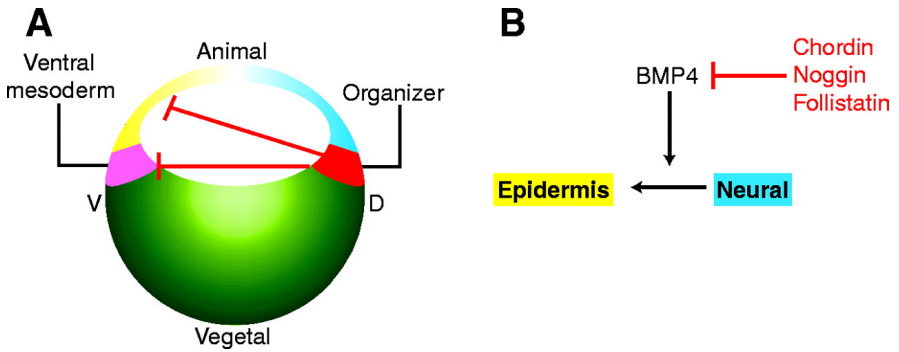


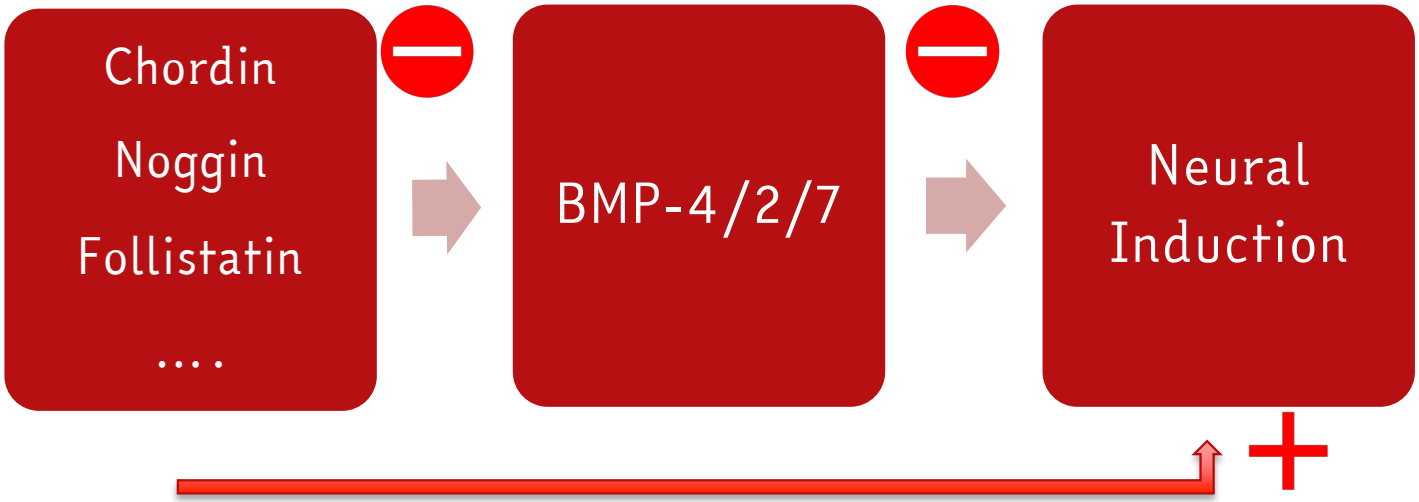
BMP Antagonists Expressed in Spemann's Organizer



Xnr3 = Xenopus nodal-related-3

Dorsal is to the right with the animal pole toward the top of the figure





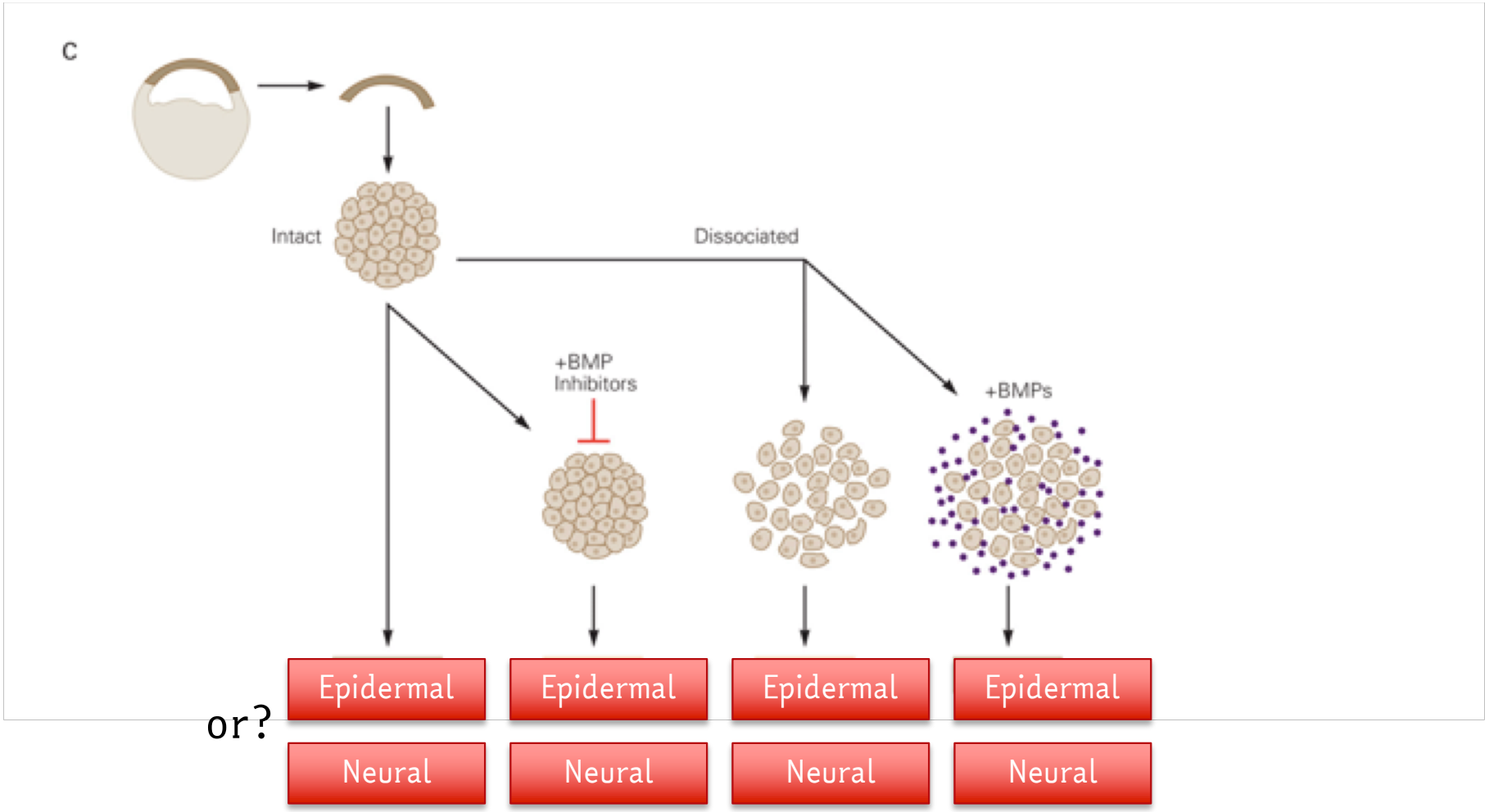
All potent extracellular inhibitors of TGFβ family signaling bind with high affinity to the ligands and prevent them from activating their cognate receptors

TABLE 1 | Secreted Inhibitors of the BMP Pathway

Gene	Inhibits	Species	Gastrula Expression†	Features-Comments	References
Chordin	BMP-2,4,7	Mouse *Xenopus* Zebrafish Chicken	Node (m) Organizer (x,z) Node and rostral mesendoderm (c)		26 30 28 31
CHL/chordin-like	BMP-4,5,6	Mouse	No	3 CR domains	32
Noggin	BMP-2,4,7 GDF-5	Mouse *Xenopus* Zebrafish	Node (m) Organizer (x,z) Axial mesendoderm (c)	3 noggin-like genes found in Zebrafish	25 33 34 35 36 37
Follistatin	BMP-2,4,7,11 GDF-8,11 Activin	Mouse *Xenopus* Chick	Node (m) Organizer (x) Node, mesendoderm, caudal neural plate (c)		27 38 39 40 37
FSRP proteins: FLRG, Flik	BMP-2,6,7 Activin	Mouse Chicken	FLRG: e7.0 by Northern (m) Flik-1: node (c)	Follistatin related	41 42 43 44 45
Cerberus	BMP-4 xNr-1,2 Wnt-8	*Xenopus* Mouse (Cer1) Chicken	Anterior endoderm (x) Anterior visceral endoderm (m) Hypoblast, Ant. Endoderm, Prechordal plate (c)		46 47 48 49 50

TABLE 1 | Secreted Inhibitors of the BMP Pathway

Gene	Inhibits	Species	Gastrula Expression†	Features-Comments	References
Coco	BMP-4 Activin xNr-1 Wnt-8	*Xenopus*	Gradient from animal to vegetal Strongest expression in ectoderm	Cerberus/dan related	51
Dan	BMP-2,4,7 GDF-5,6,7	Mouse *Xenopus*	No No		52 50 53 54
Caronte	BMP-4,7	Chicken	Mesoderm flanking the node		55 56
Lefty1 Lefty2	Nodal	Mouse Chicken	Notochord/midline (Lefty1; m,c) Mesoderm (Lefty2; m,c)		57,58
Dante	ND	Mouse	Node	No full-length cDNA reported	53
PRDC	ND	Mouse	ND	Cerberus/Dan-like	59
Drm/Gremlin	BMP-2,4	Mouse *Xenopus*	No No		50 60 53
Neuralin-1	BMP-4,5 TGF-β1,2	Mouse	Emerging neural plate	3 CR domains	61 32
CTGF	BMP-4 TGF-β1	*Xenopus*	Weak expression	1 CR domain	62
Kielin	ND	*Xenopus*	Axial mesoderm	27 CR domains	63


C
Intact
Dissociated
+BMP
Inhibitors
+BMPs
Epidermal
Epidermal
Epidermal
Epidermal
Neural
Neural
Neural
Neural

or?

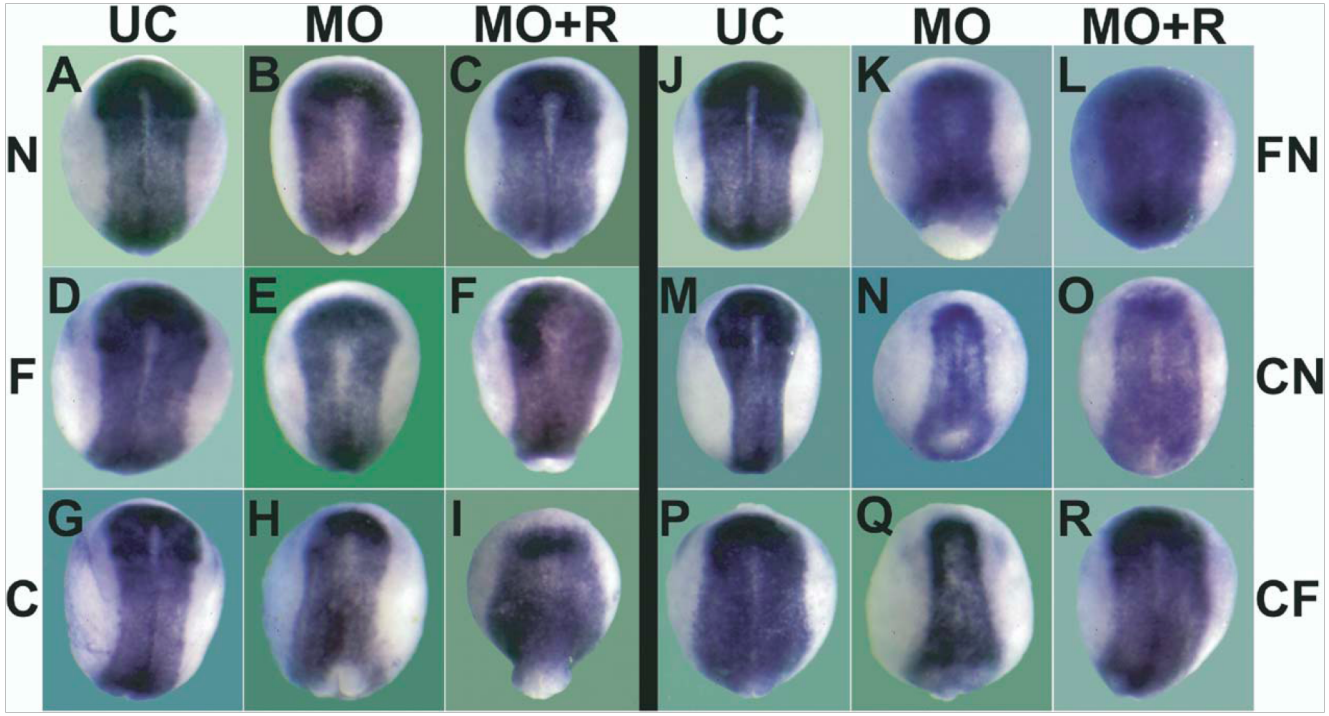
Mechanistic demonstrations

An authentic Neural Inducer should …

- …be at the right place at the right time → **LOCATION** ✓
- …when signal is blocked – no response → **NECESSITY**
- ….be able induce the response peraphs ectopically → **SUFFICIENCY** ✓

Loss of function assay with Morpholino oligonucleotides

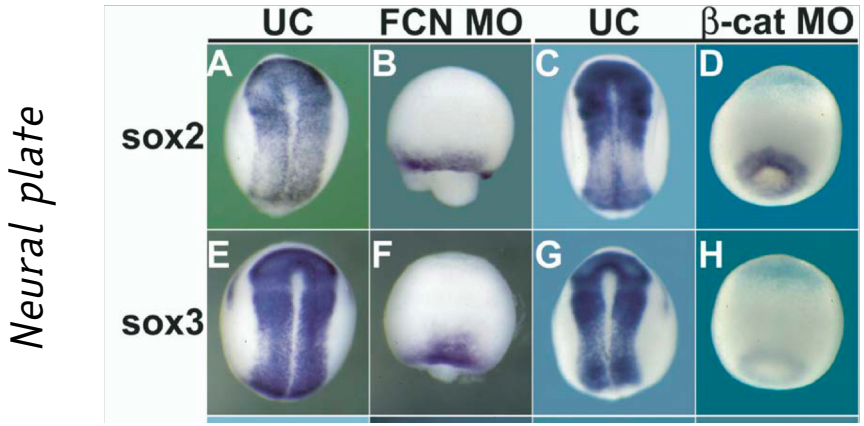
Sox2 expression in neurula (st 14–15) embryo



F = Follistatin, C = Chordin, N = Noggin, UC = uninjected sibling control embryos, MO = morphant, and MO + R = morphant rescued with **pufferfish** noggin mRNA.

Khokha et al....R. Harland, Developmental Cell 2005

Molecular redundancy



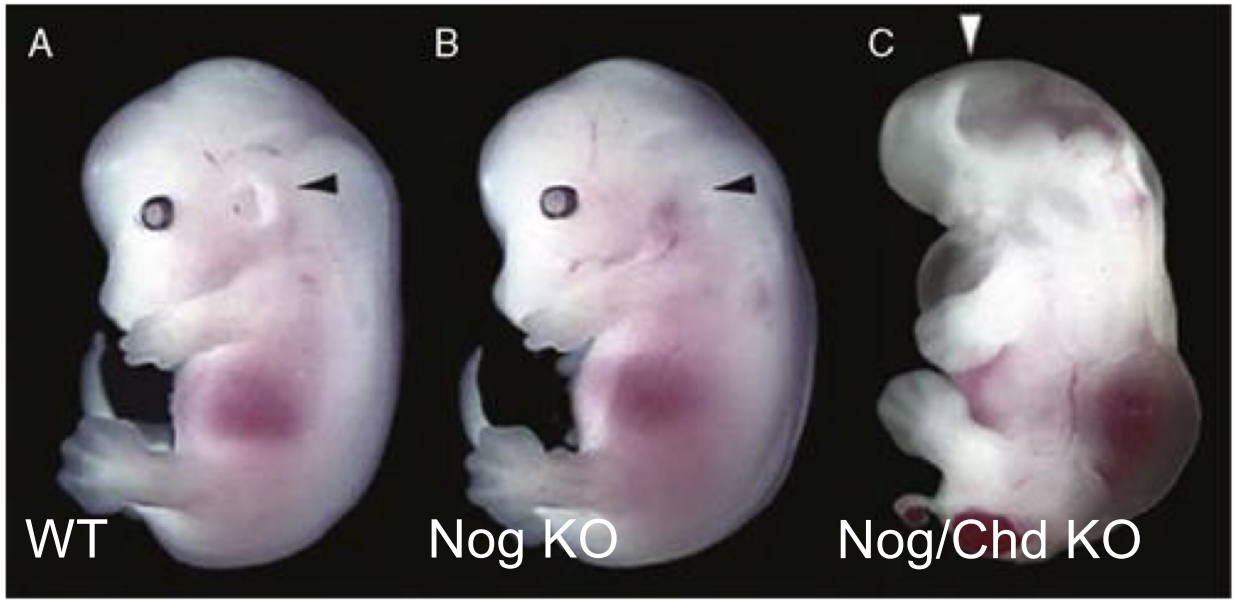
Beta-catenin MO – prevent formation of the Speman organizer

Deletion of 3 BMP antagonists from Spemann's organizer leads to a chatastrophic loss of dorsal structure: lack a morphological neural plate at the neural stage and dorsal mesoderm structures

→ Conclusive in vivo evidence that BMP inhibitors are essential for neural induction

Khokha et al., Developmental Cell 2005

Molecular redundancy



Genetic redundancy

to be taken into account in programming LOF approaches

What functional meaning?

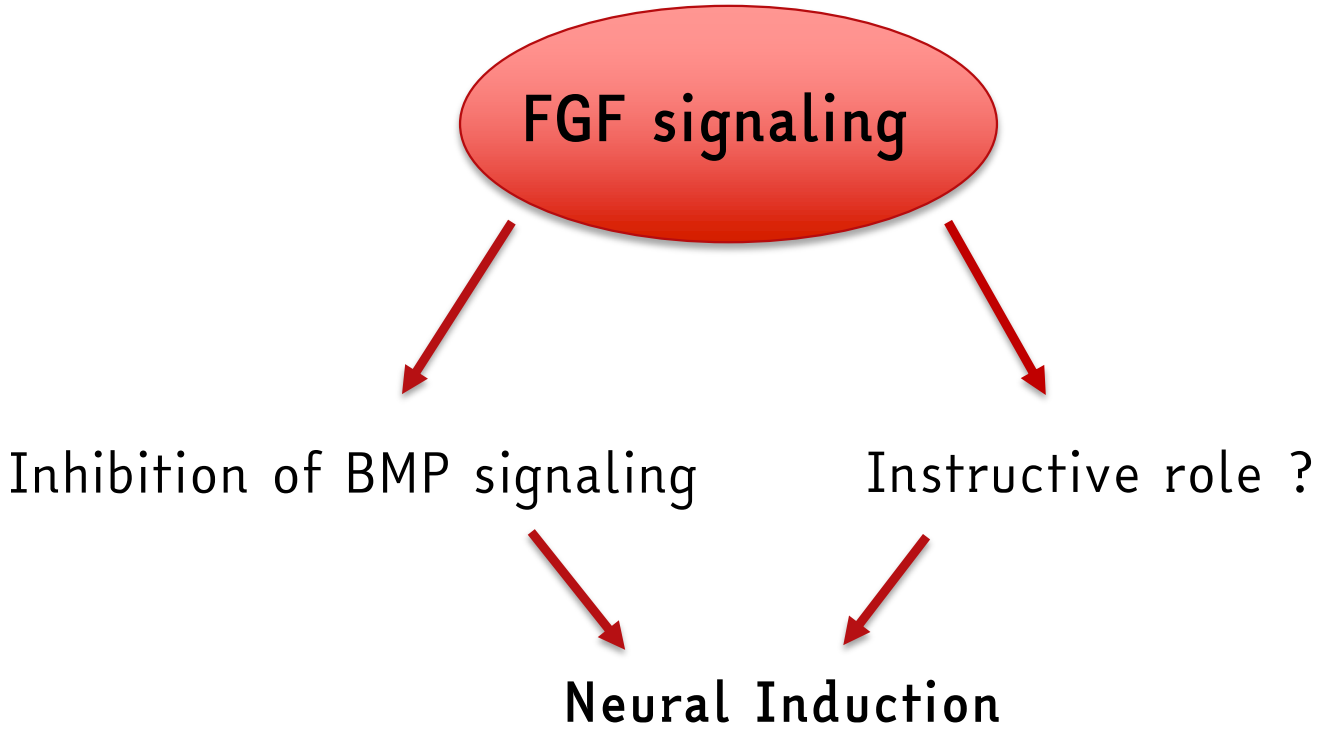
Bachiller et al., 2000

Is BMPs inhibition sufficient for neural induction?

Several evidences from different species indicate that the default model may be too simplistic to describe neural induction…

- *Blocking BMP signalling cell autonomously by electroporating SMAD6 is not sufficient to induce Sox3 expression in competent chick epiblasts*
- *Data from fish – frog – chick… indicate FGF signaling restricts BMP gene expression and is required for expression of BMP inhibitors*
- *In the urochordate Ciona intestinalis, FGF is an important neural inducing signal*

Beyond the default model



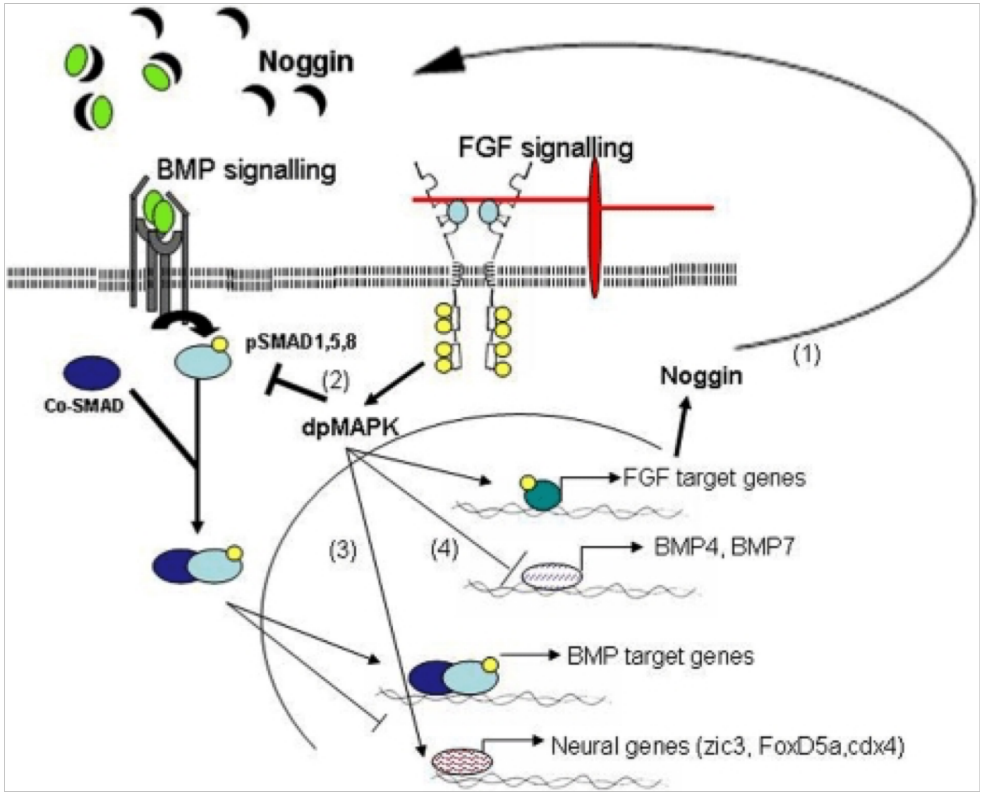
How can FGF signalling impact on neural induction?

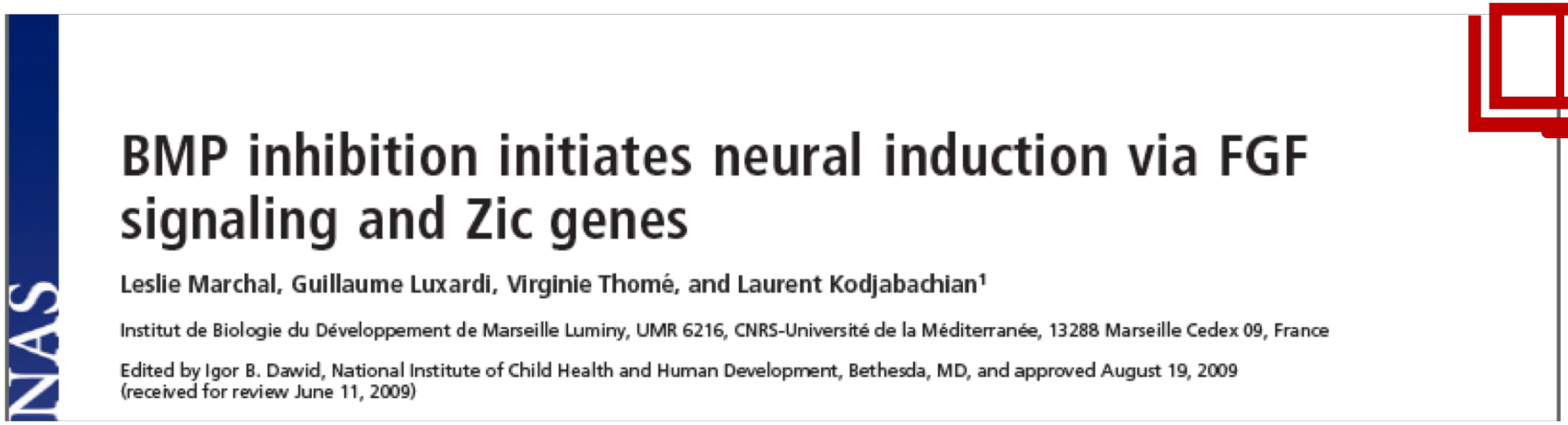
(1) is required for the expression of Noggin, which acts outside the cell to bind and inhibit the activity of BMP ligands

(2) results in the phosphorylation of SMAD1, 5, 8 in a central domain, which inhibits its ability to move to the nucleus and activate the transcription of BMP target genes

(3) FGF signalling can directly activate the transcription of a set of neural genes

(4) FGF can inhibit the expression of genes coding for BMP ligands





PNAS

BMP inhibition initiates neural induction via FGF signaling and Zic genes

Leslie Marchal, Guillaume Luxardi, Virginie Thomé, and Laurent Kodjabachian[1]

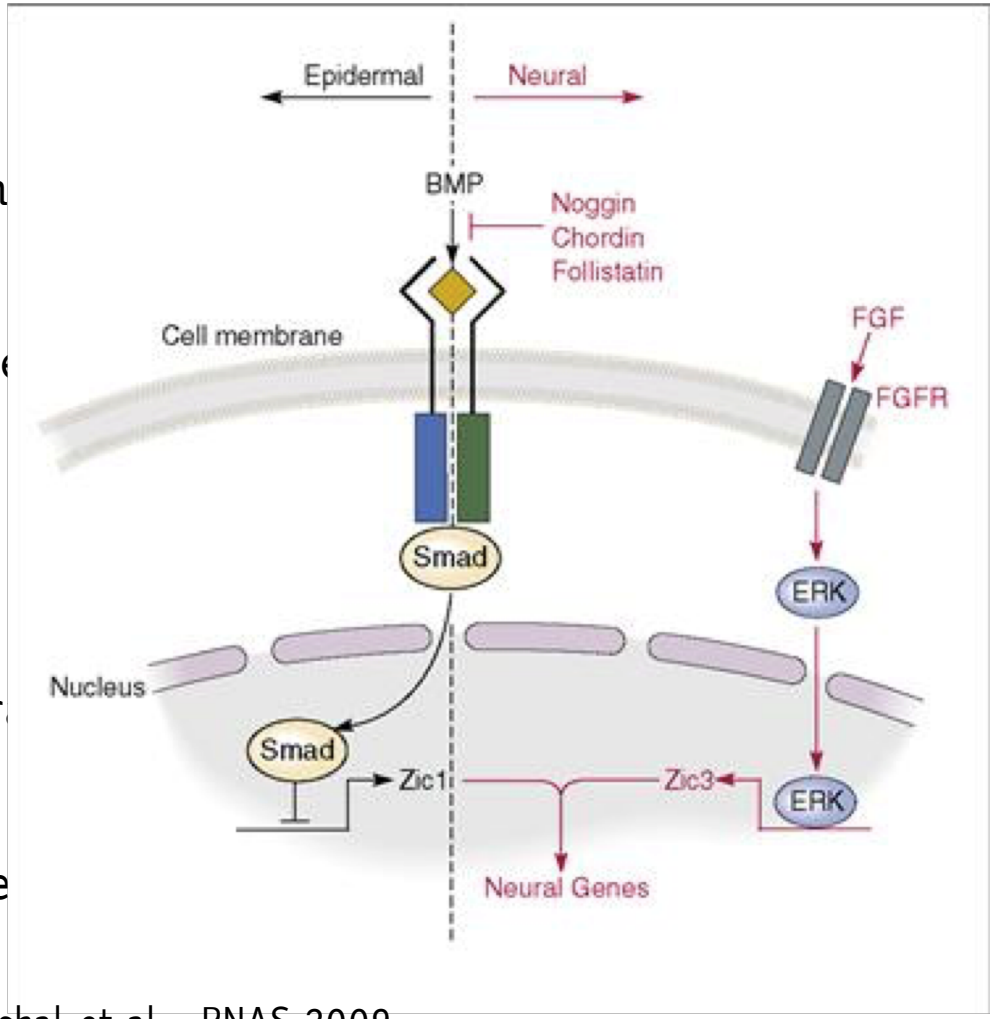
Institut de Biologie du Développement de Marseille Luminy, UMR 6216, CNRS-Université de la Méditerranée, 13288 Marseille Cedex 09, France

Edited by Igor B. Dawid, National Institute of Child Health and Human Development, Bethesda, MD, and approved August 19, 2009
(received for review June 11, 2009)

Article to read

- The **Zic** family of zinc-finger proteins plays a crucial role in neural development - They act as transcriptional regulators and control the initial phase during which ectoderm differentiates into neuroectoderm

- Validation of the default model of neural induction
- Neural induction by BMP inhibition depends on the presence of FGF activity
- FGF is downstream of BMP inhibition to initiate the neural program
- BMP inhibition and FGF signaling are both important and act sequentially
- FGF signaling plays an instructive role in neural induction
- Both Zic1 and Zic3 are required to initiate the neural program (they act redundantly)

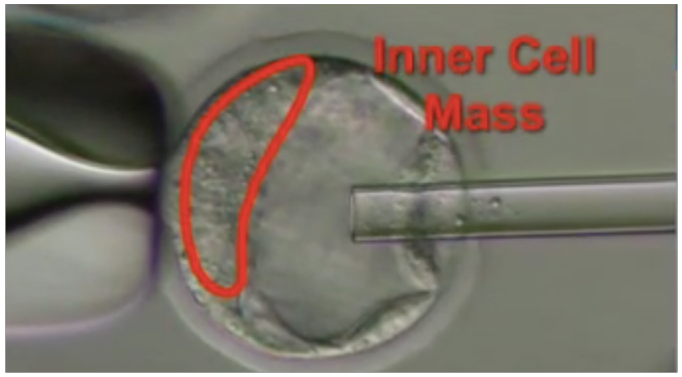


Marchal et al., PNAS 2009

Neural induction in mammalian ESCs

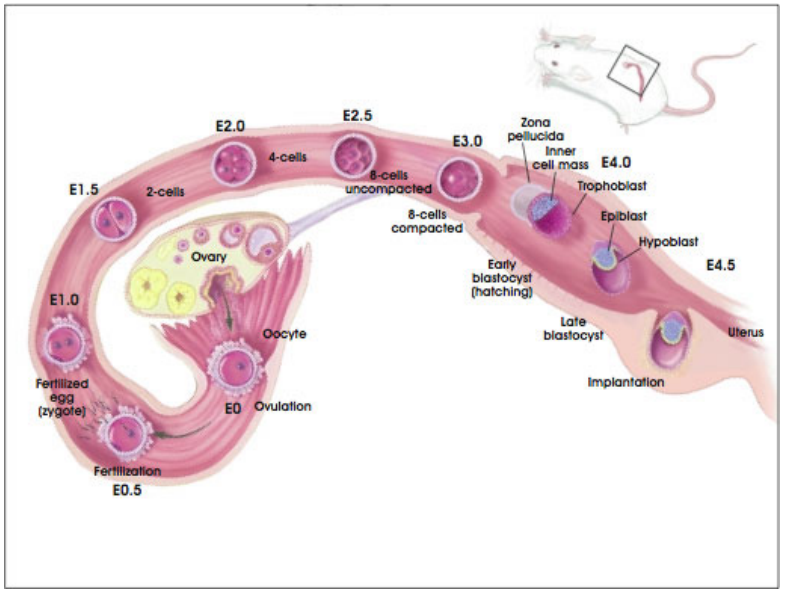
ESCs = embryonic stem cells
1981 Gail Martin
Martin Evans and Matthew Kaufman

Mouse ESCs derived from the inner cell mass of the blastocyst of preimplantation embryos

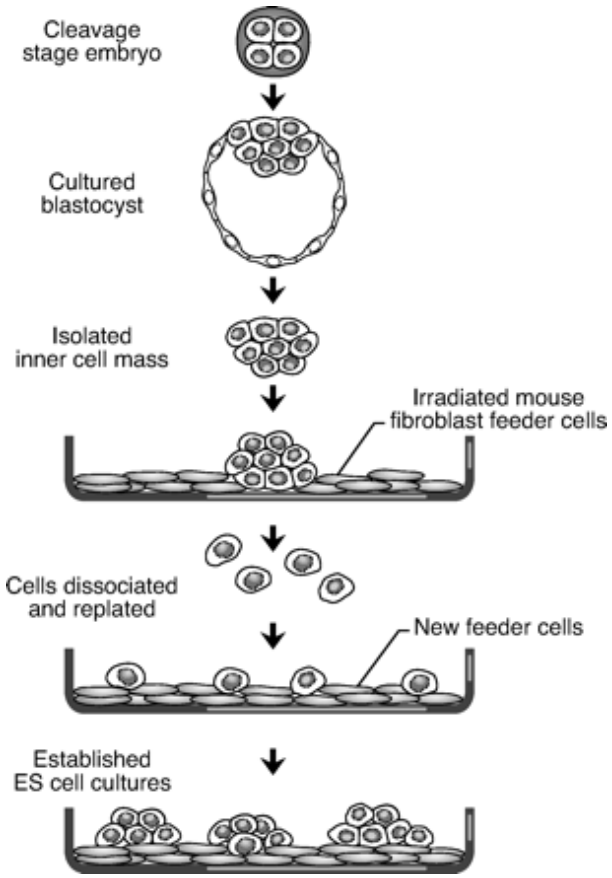


Self-renewal
Pluripotency
Express embryonic TFs
(i.e. Oct-4; Sox2; Nanog)

ESCs: an in vitro platform to test hypoteses and investigate mechanisms controlling embryonic fate determination



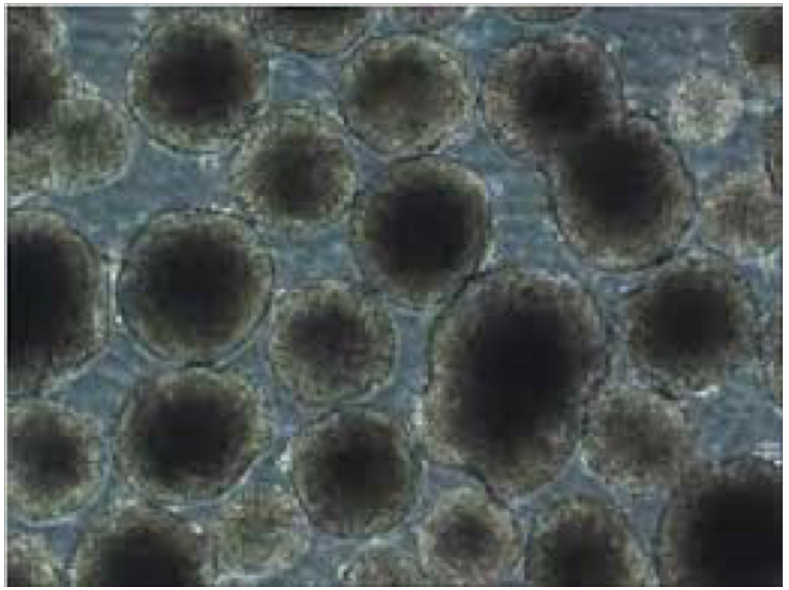
Mouse ES cell culture



Feeder layer was crucial for **isolation** of ES from blastocyst

addition of **leukemia inhibitory factor (LIF)** replaces the need for a feeder (LIF is required for maintenance in **undifferentiated** state)

LIF withdrawal and growth of ES cells in **suspension** result in **embryoid bodies** and differentiation



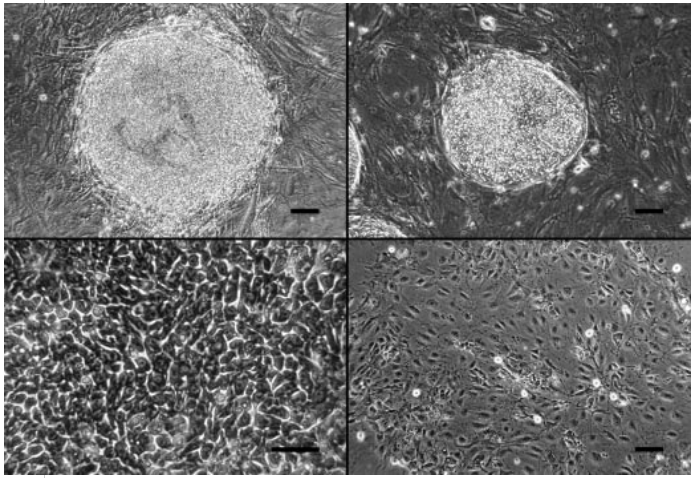
Science-1998

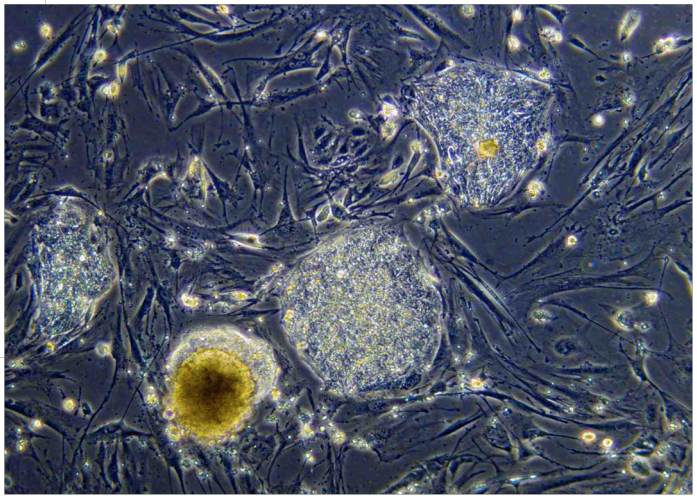
REPORTS

Embryonic Stem Cell Lines Derived from Human Blastocysts

James A. Thomson,* Joseph Itskovitz-Eldor, Sander S. Shapiro, Michelle A. Waknitz, Jennifer J. Swiergiel, Vivienne S. Marshall, Jeffrey M. Jones

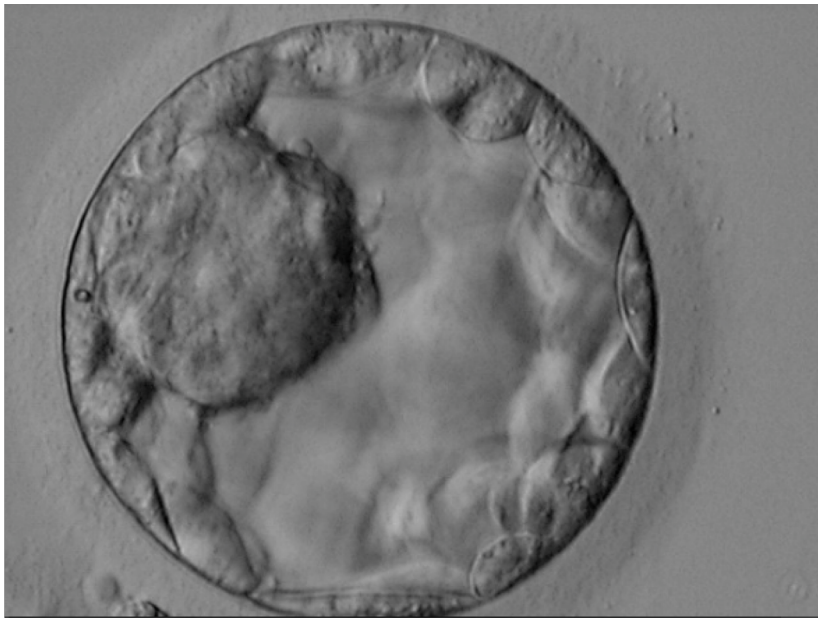
Human blastocyst-derived, pluripotent cell lines are described that have normal karyotypes, express high levels of telomerase activity, and express cell surface markers that characterize primate embryonic stem cells but do not characterize other early lineages. After undifferentiated proliferation in vitro for 4 to 5 months, these cells still maintained the developmental potential to form trophoblast and derivatives of all three embryonic germ layers, including gut epithelium (endoderm); cartilage, bone, smooth muscle, and striated muscle (mesoderm); and neural epithelium, embryonic ganglia, and stratified squamous epithelium (ectoderm). These cell lines should be useful in human developmental biology, drug discovery, and transplantation medicine.





Important to know!

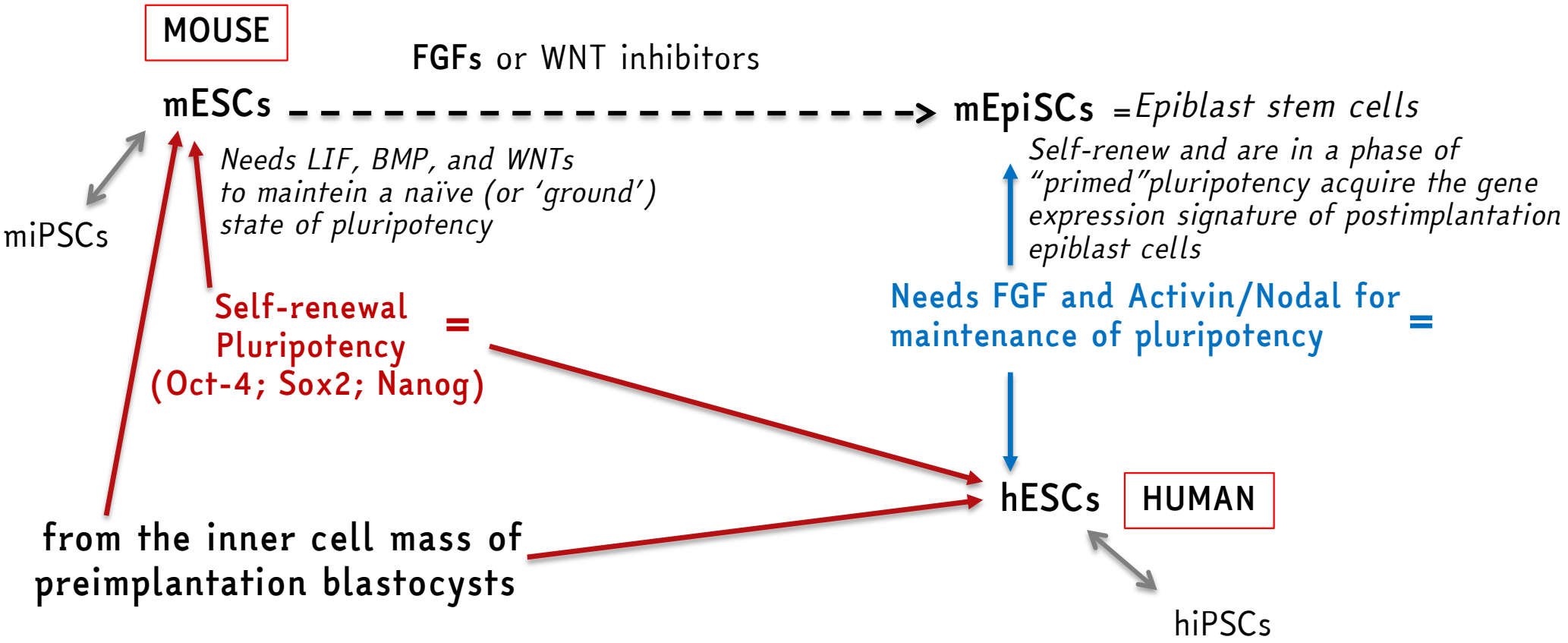
Human ES cells do not come from aborted fetuses but derive from leftover in vitro fertilization (IVF) embryos
(around 5 days after fertilization – no tissue differentiation)



One blastocyst may produce a number of cell lines that can be kept in culture for years.

Cells adapted to proliferate in tissue culture represent only a proxy for the in vivo situation (properties of cells in the embryo)

Similarities and differences (mouse vs human ESCs)



mESCs represent an early stage of development compared to hESCs

Neural Induction in Mouse ESCs

Chemically defined serum-free, feeder layer-free, low-density culture conditions are sufficient for neural differentiation of ES cells

ARTICLE Neuron 2001

Direct Neural Fate Specification from Embryonic Stem Cells

A Primitive Mammalian Neural Stem Cell Stage Acquired through a Default Mechanism

Abstract

Little is known about how neural stem cells are formed initially during development. We investigated whether a default mechanism of neural specification could regulate acquisition of neural stem cell identity directly from embryonic stem (ES) cells. ES cells cultured in defined, low-density conditions readily acquire a neural identity. We characterize a novel primitive neural stem cell as a component of neural lineage specification that is negatively regulated by TGFβ-related signaling. Primitive neural stem cells have distinct growth factor requirements, express neural precursor markers, generate neurons and glia in vitro, and have neural and non-neural lineage potential in vivo. These results are consistent with a default mechanism for neural fate specification and support a model whereby definitive neural stem cell formation is preceded by a primitive neural stem cell stage during neural lineage commitment.

Conversion into nestin expressing neural precursors (enhanced by inhibition of BMP signaling with Noggin or Cerberus and Smad4 KO ESCs)

Is there a Role for FGF Signaling in Neural Induction in Mouse ESCs ?

FGF signaling manipulations on mESCs suggest a role for FGF...

BUT:

- mESCs require FGF signaling to progress to a primed state of pluripotency before they acquire the competence for neural induction
- FGF signaling has been shown to inhibit rather than promote neural induction in EpiSCs
- Inhibition of the TGFβ/BMP signaling promotes neural commitment from EpiSCs

FGF signaling possibly regulates the competence of mESCs for germ layer differentiation, rather than neural induction per se

Neural Induction in Human ESCs/iPSCs and the Role of FGF Signaling

In the absence of exogenous morphogens, hESC colonies take on a neural fate in line with the default model

FGF?

- small-molecule inhibitors of FGF signaling reduce the number of cells expressing PAX6 (but FGF inhibitors were not added in the initial 4 days of differentiation)

- FGF increases the size of neural colonies without changing the efficiency of neural induction

- neuralized hESCs displayed low levels of BMP-SMAD1/5/8 signaling, presumably because of the high-level expression of several soluble BMP antagonists

FGF → survival and/or proliferative role in the early neuroepithelium