Cell Fate I
(Determination & Differentiation)

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Definitions

- Fate or Phenotype = cell type or characteristics of a cell (position, form & function)

- Differentiation = process of developing the characteristics of a particular fate

States Leading to Differentiation during Neural Development

- Competence – the ability of a cell to acquire a certain fate if exposed to the proper inducers

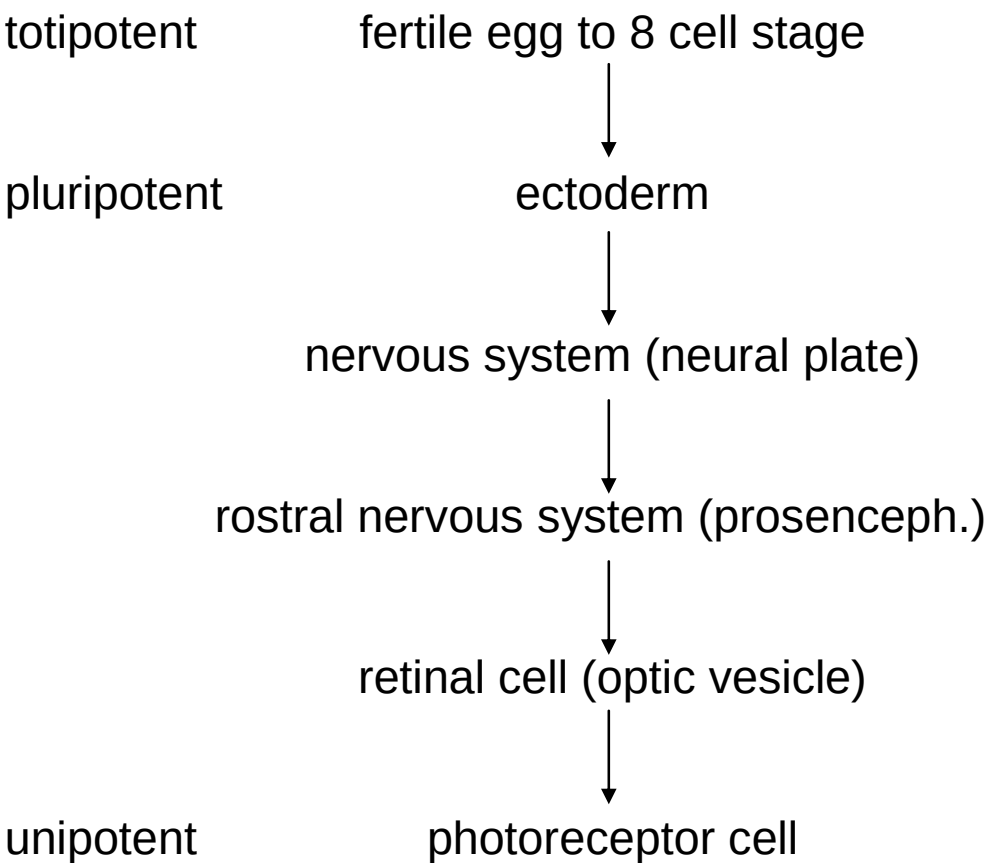
- Specified – cell has been exposed to inducers and may have started along a specific path of development, but a change in the environment can still alter the ultimate fate of the cell

- Determined or Committed – cell has a commitment to a particular fate, which will be maintained even if the cell is exposed to different inducers

- Differentiated – cell expresses the characteristics appropriate for a particular fate

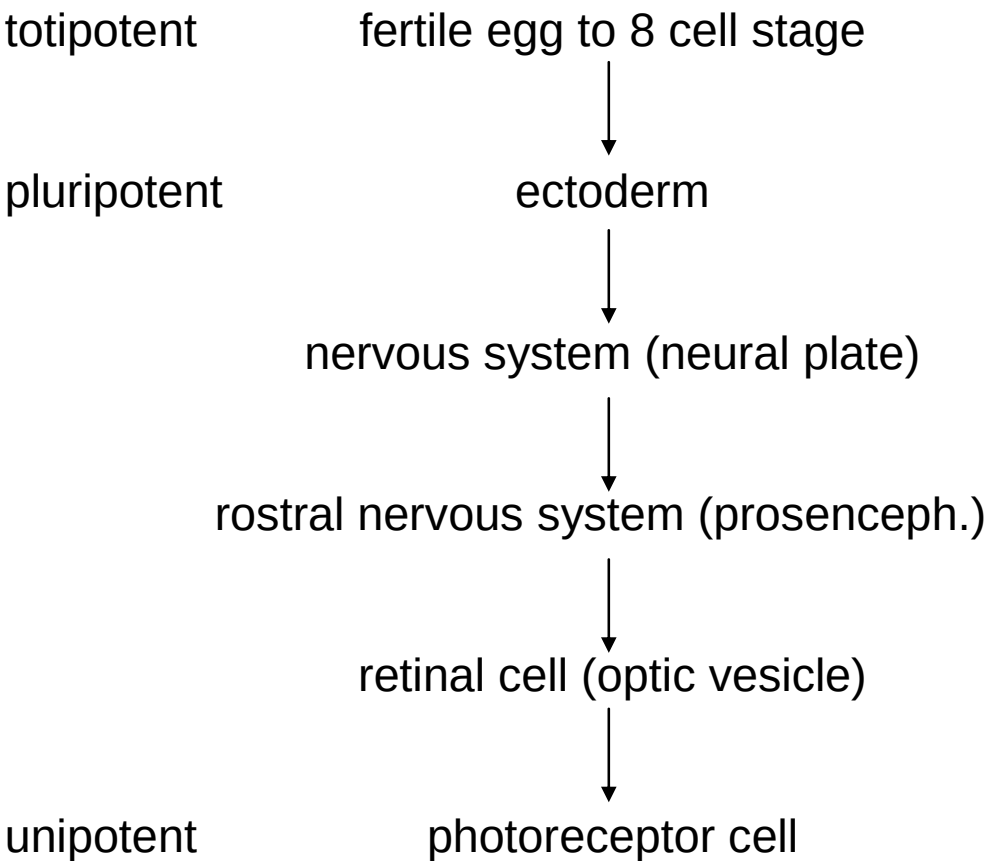
Determination of cell fate is due to the sequential restriction of possible fates.

- e.g. determination of retinal photoreceptor cell fate:



Determination of cell fate is due to the sequential restriction of possible fates.

- Fate restrictions are unidirectional.



What determines cell fate?

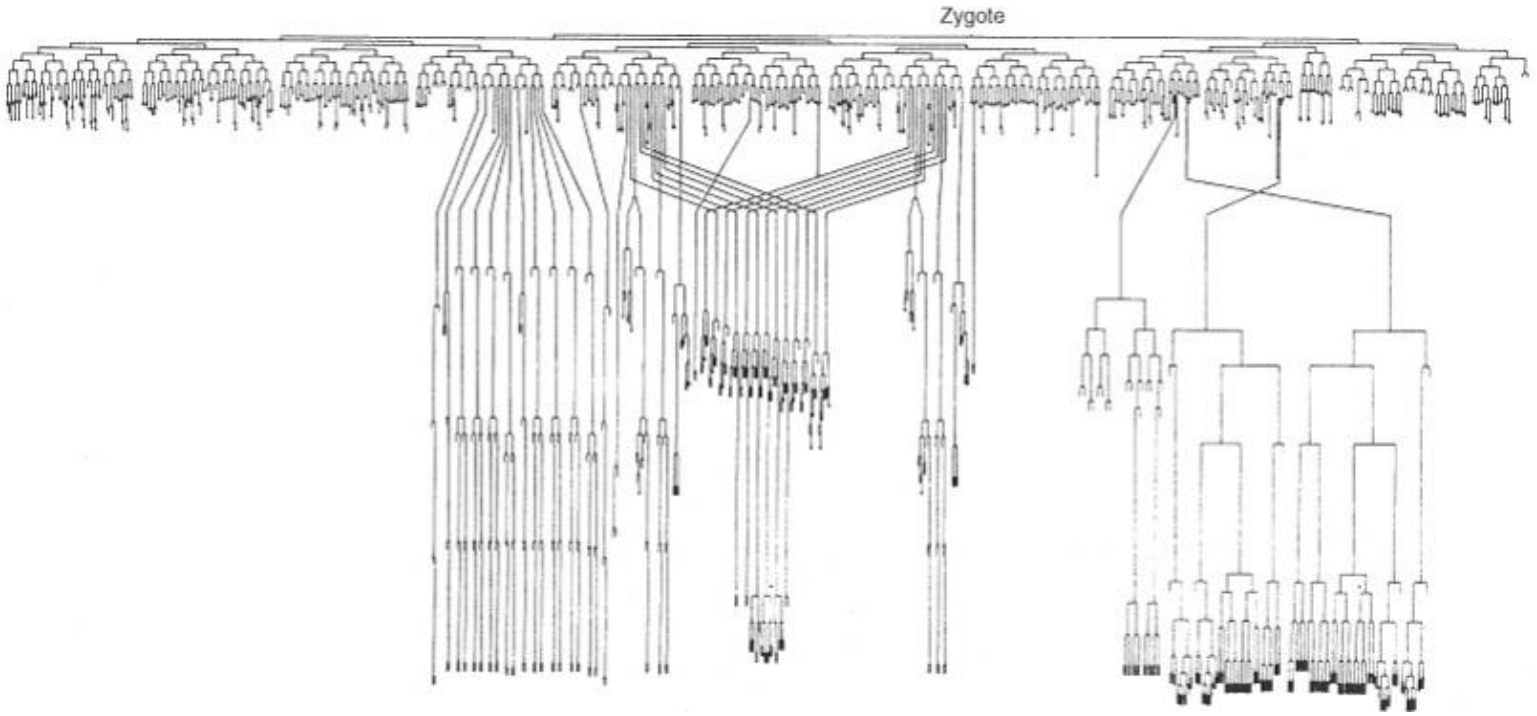
- Intrinsic program – inherited fate
- Extrinsic cue - features in the environment to which a cell can respond with a change in potential fate

  [Extrinsic cues induce intrinsic changes.]

Intrinsic program determines cell fate in C. elegans.

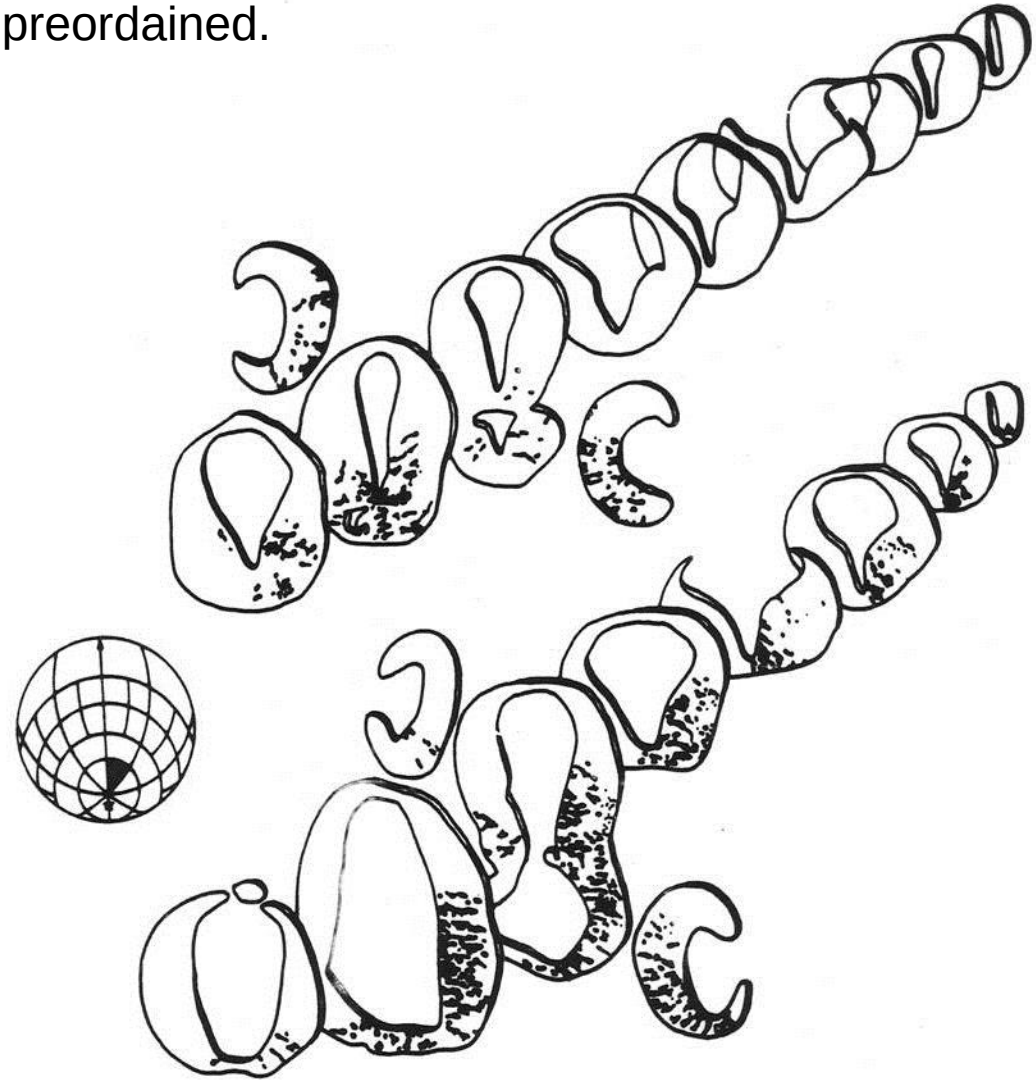
- Cell fate is determined by an invariant lineage relationship.

- Elimination of a progenitor cell eliminates all the cells that would have developed in the downstream lineage of that cell.



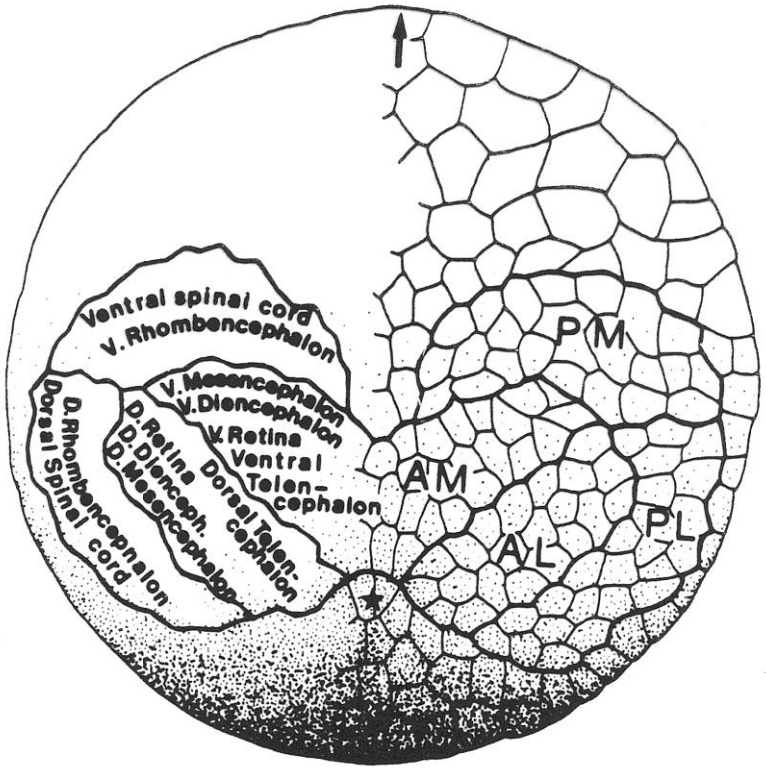
Intrinsic and extrinsic mechanisms function in vertebrate development.

- Lineage tracing in early frog embryo showed that lineage is predictive of cell fate, but cell fate is not rigidly preordained.



Intrinsic and extrinsic mechanisms function in vertebrate development.

- By the 512 cell blastula, there are 7 pair-groups of founder cells. Destruction of a portion of a single founder group will have minimal effect on the outcome of development. Destruction of an entire founder group will result in the absence of the particular structures that arise from that founder group.

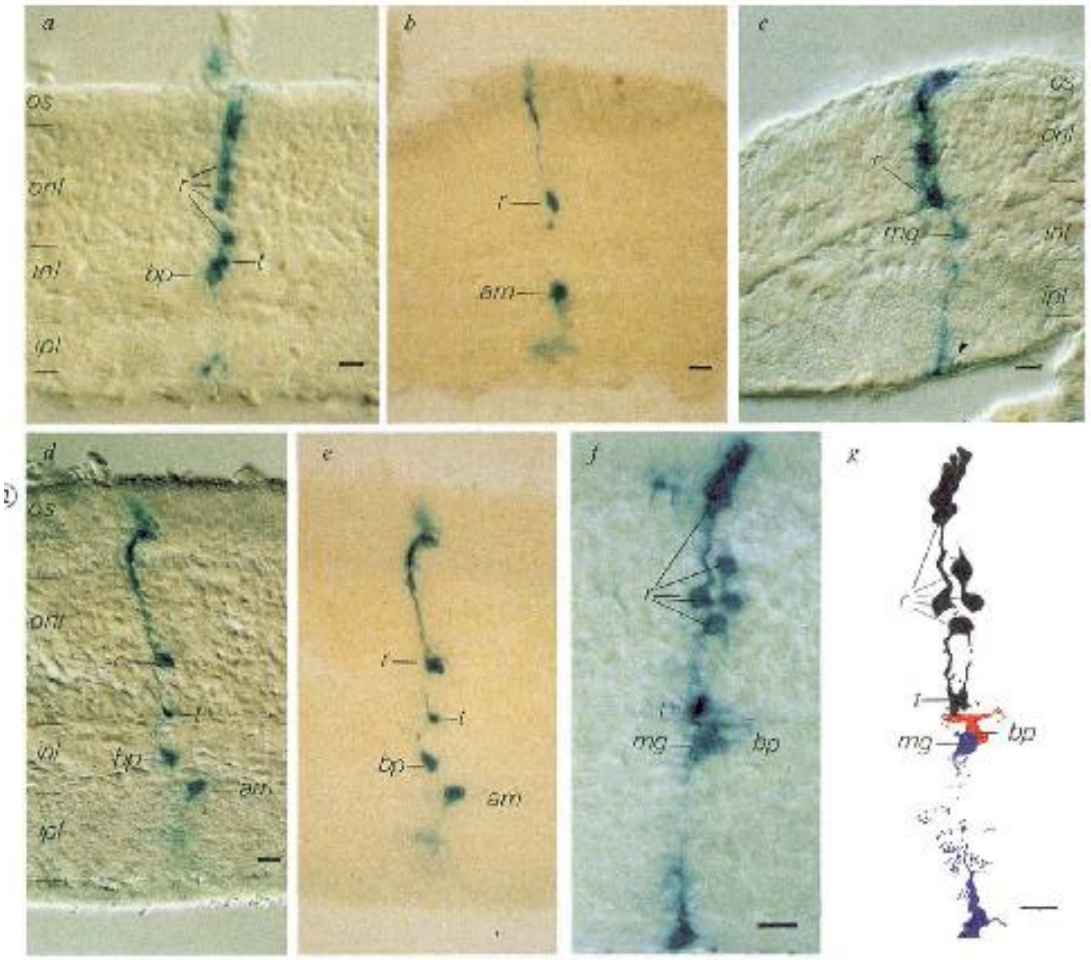


Intrinsic and extrinsic mechanisms function in vertebrate development.

- Changes in transcription are first seen after the 512 cell stage.
- Maternal mRNA is asymmetrically distributed during the early cell divisions.
- Thus, early differences in competence are determined by intrinsic mechanisms.

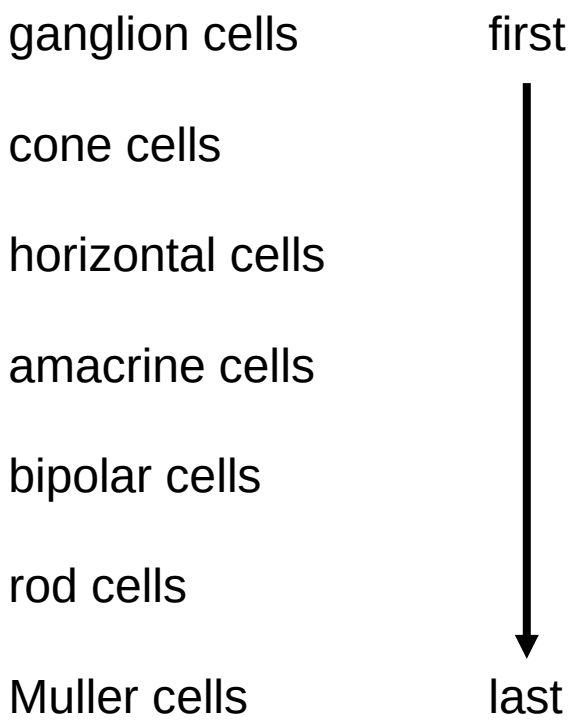
Intrinsic and extrinsic mechanisms function in vertebrate development.

- Lineage tracing later in development showed that individual progenitor cells can produce multiple cell types in no rigidly fixed pattern.
  e.g. lineage tracing in retina



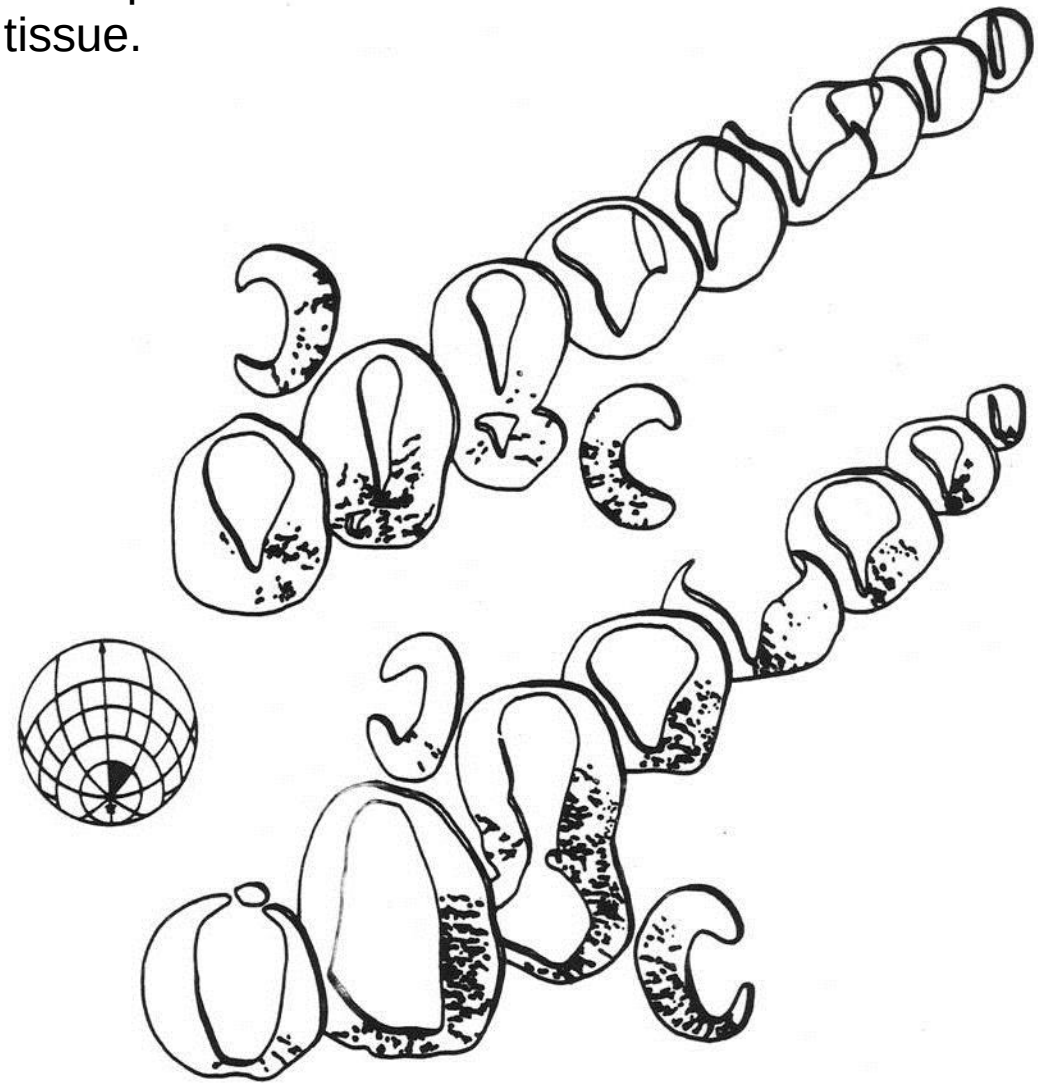
There is a sequence to production of the different cell types in each domain of the nervous system.

e.g. In retina:



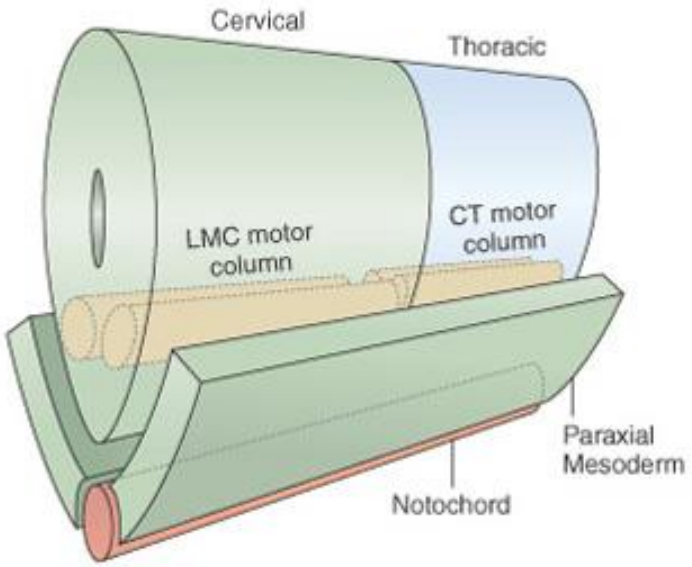
Position alone is not the same as determination.

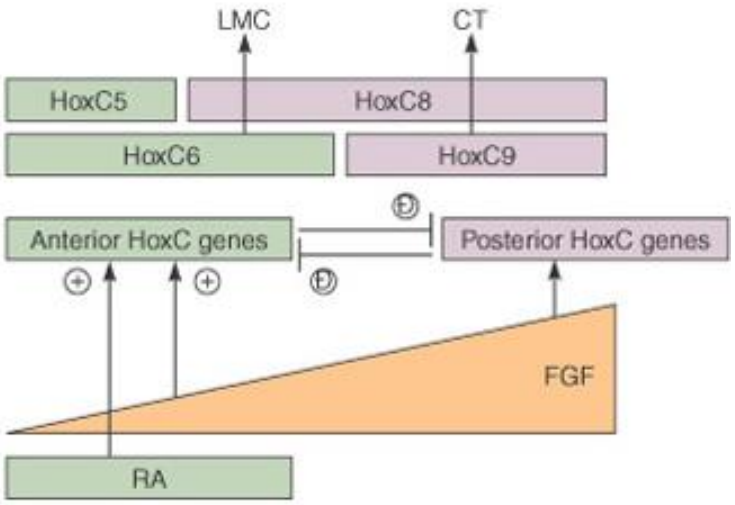
- Transplantation can reveal the determined state of a tissue.



Factors that induce regional differences determine the initial cell fate in each domain.

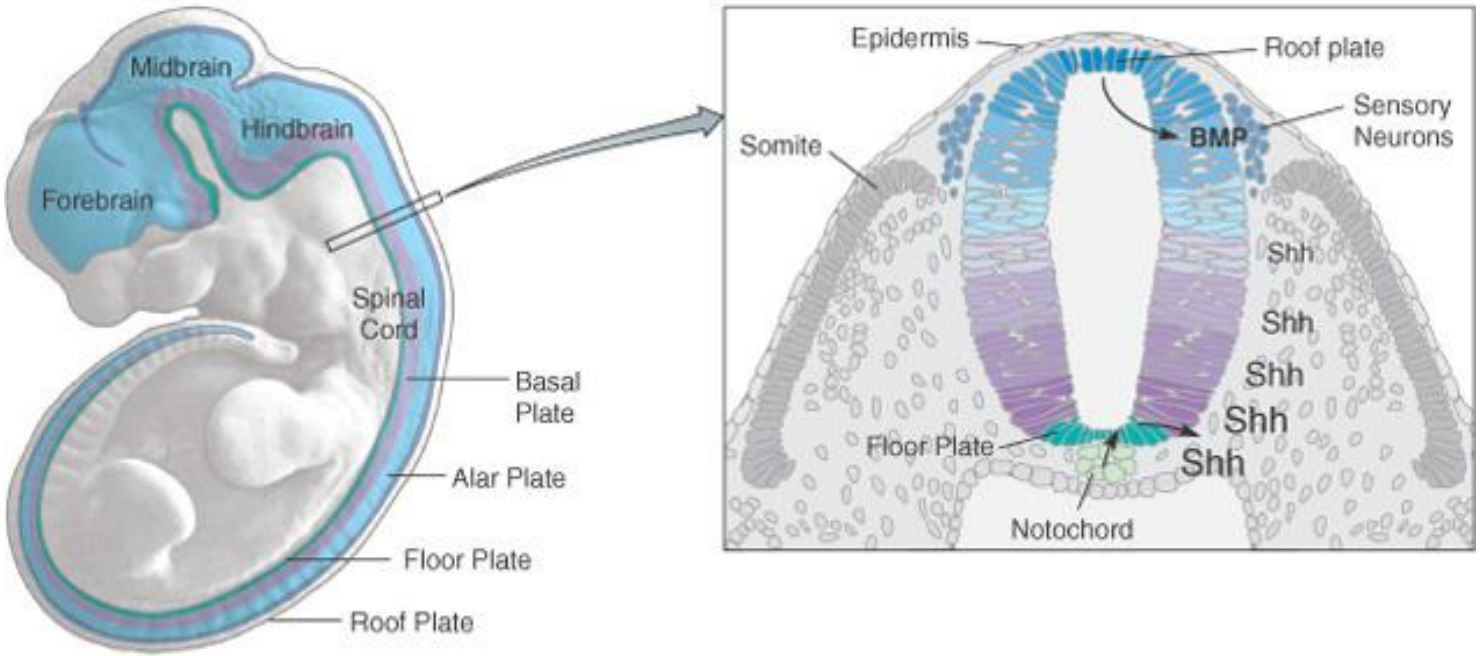
- Anterior-posterior concentration gradients of factors including fibroblast growth factor (FGF) and retinoic acid (RA) specify regional differences along the anterior-posterior axis.





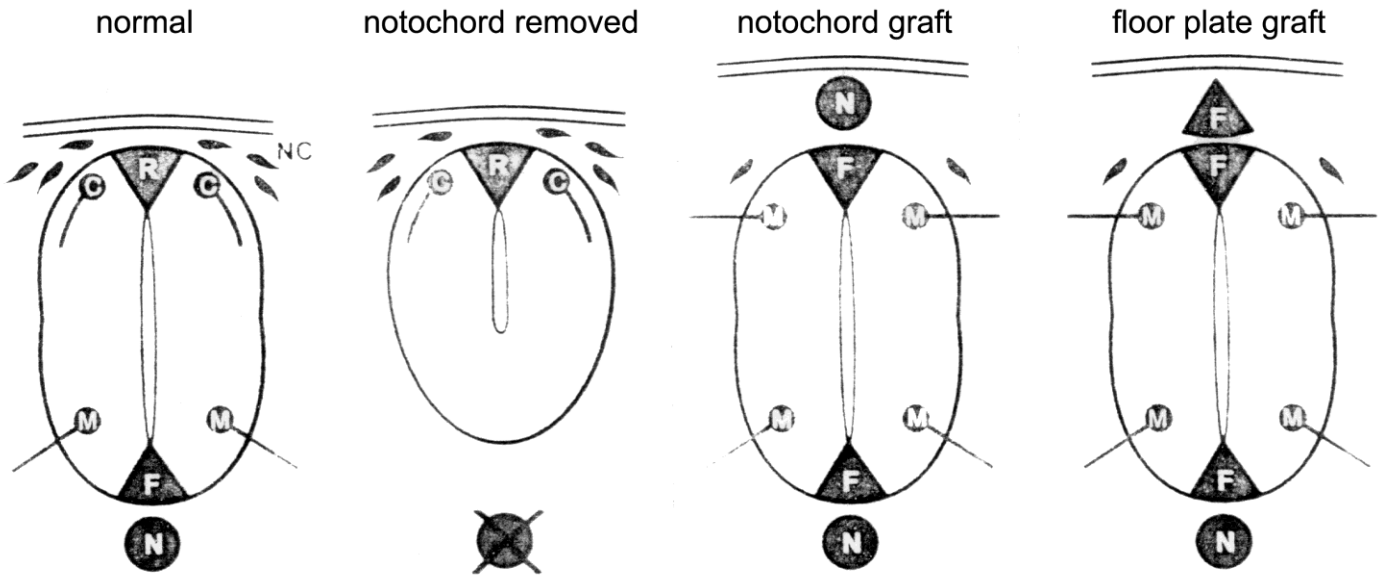
Factors that induce regional differences determine the initial cell fate in each domain.

- Sonichedgehog (Shh) is expressed initially by notochord and later by floor plate.



Factors that induce regional differences determine the initial cell fate in each domain.

- Early removal of notochord resulted in no floor plate or motor neurons.
- Transplantation of an additional notochord or floor plate induced a second floor plate and more motor neurons.

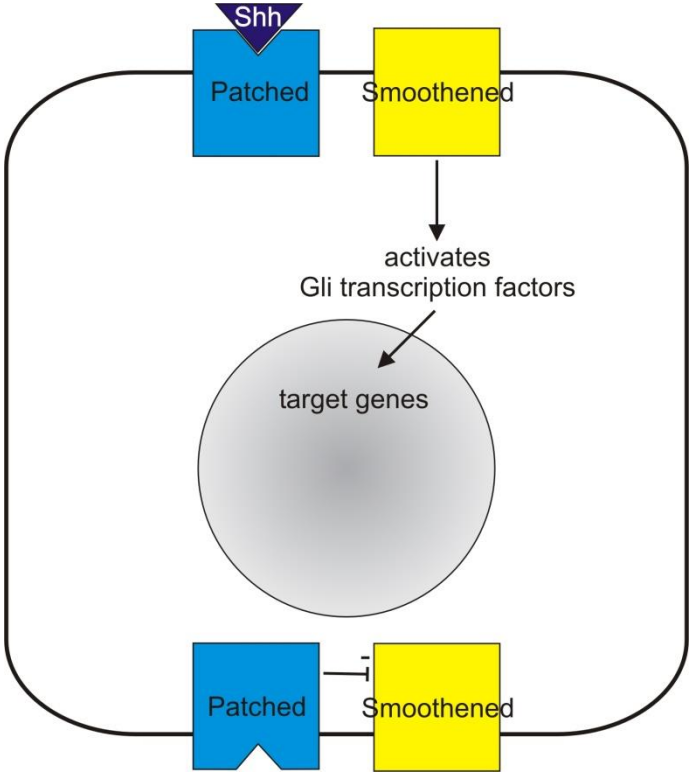


Factors that induce regional differences determine the initial cell fate in each domain.

- COS cells expressing Shh implanted next to the neural tube induced floor plate and motor neurons.
- Antibodies to Shh blocked notochord induction of ventral structures.
- High concentration of Shh induces floor plate; lower concentration induces motor neurons.
- Notochord induces floor plate when in contact with the neural plate. After tube closure, notochord moves ventrally, and motor neurons are induced by floor plate Shh.

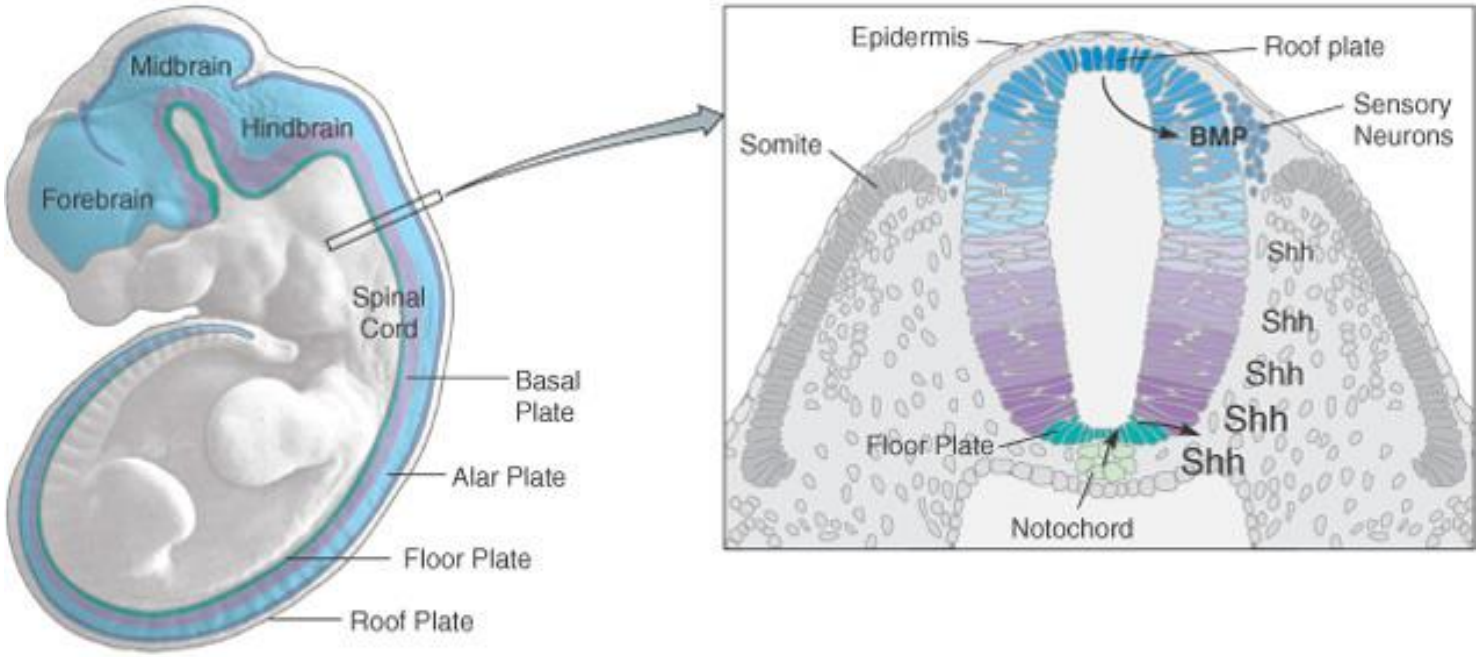
Factors that induce regional differences determine the initial cell fate in each domain.

- Shh is the ligand for Patched.
- Without Shh, Patched inhibits Smoothened.
- When Shh binds to Patched, the effect of Patched on Smoothened is terminated and Smoothened becomes active.
- Active Smoothened activates Gli transcription factors.



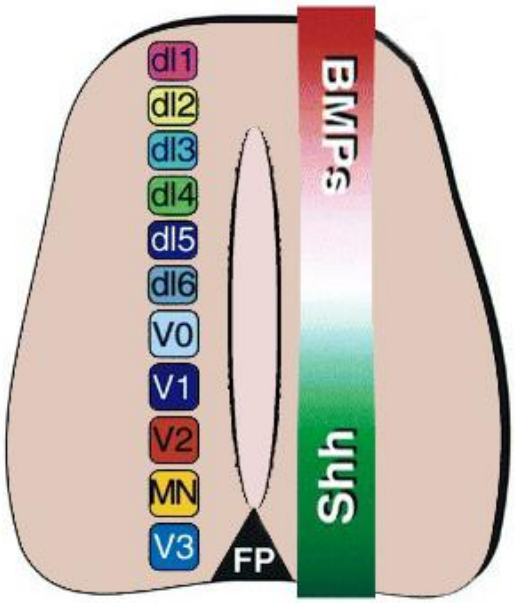
Factors that induce regional differences determine the initial cell fate in each domain.

- Bone morphogenetic proteins (BMPs) from ectoderm and dorsal neural tube induces dorsal cell fates.



Factors that induce regional differences determine the initial cell fate in each domain.

- The concentration of BMPs and Shh coupled with the nature of the anterior-posterior position determine the initial cell fates in each domain of the developing spinal cord.



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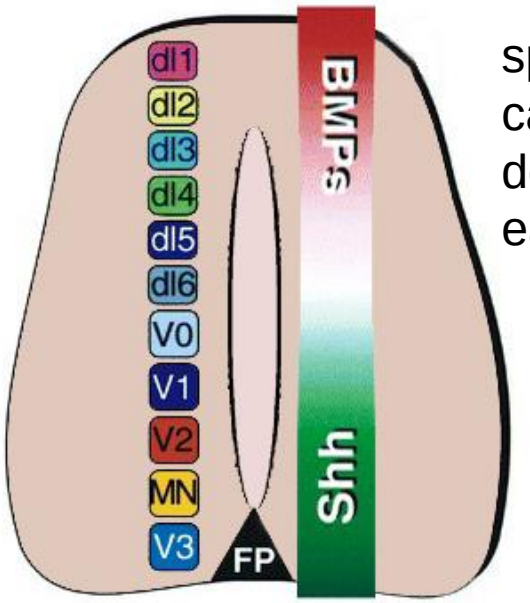


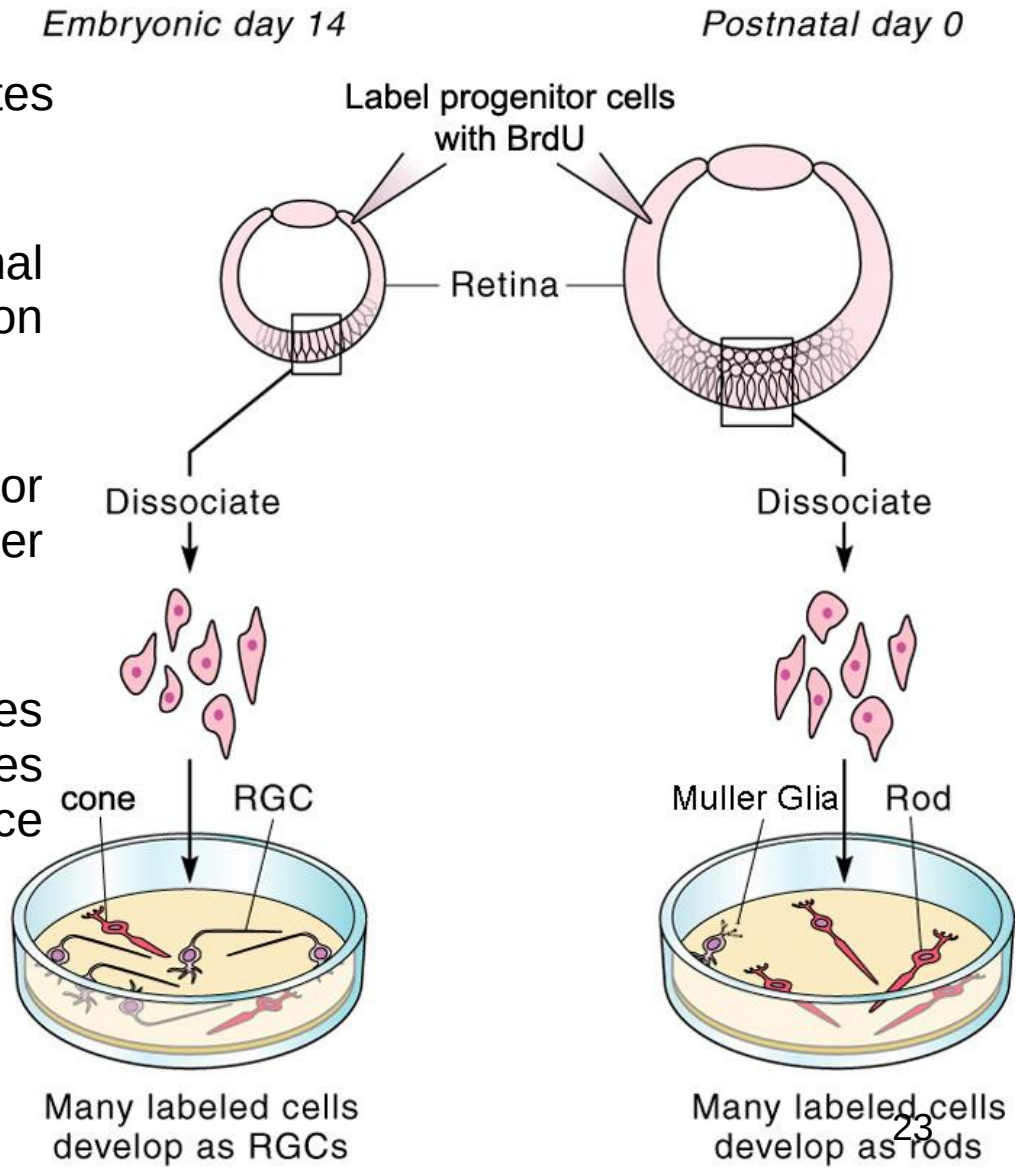
spinal cord has 31 rostral-caudal segments and 11+2 dorsal-ventral domains in each segment

Factors that induce regional differences determine the initial cell fate in each domain.

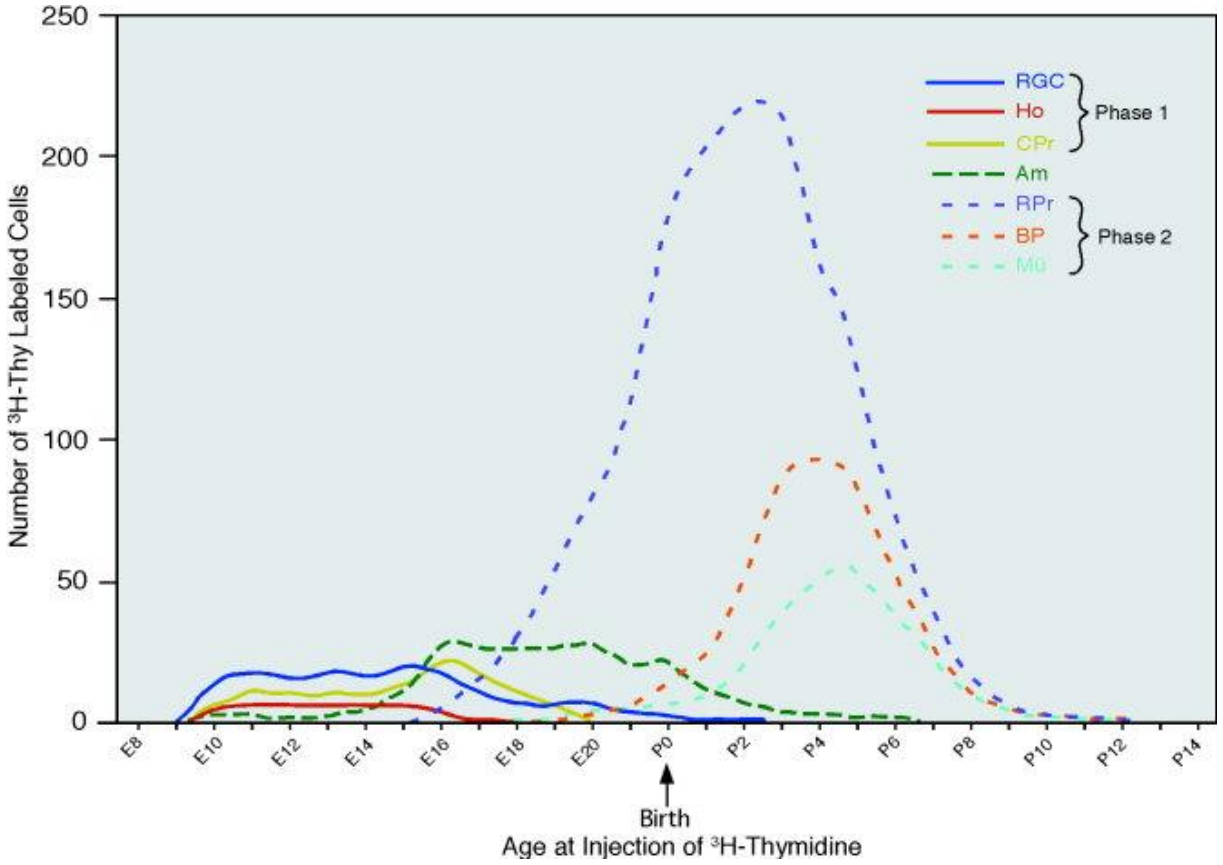
- The first cell type generated in a domain is the ‘default fate’.

Progenitor cell competence changes as development progresses.

- Dissociation of progenitor cells initiates differentiation.
- Dissociation of young retinal progenitor cells results in ganglion and cone cell differentiation.
- Dissociation of old retinal progenitor cells results in rod, bipolar and Muller glial cell differentiation.
- Production of early cell types ceases and production of later cell types starts as progenitor cell competence changes.



Timing of Cell Genesis in the Rat Retina



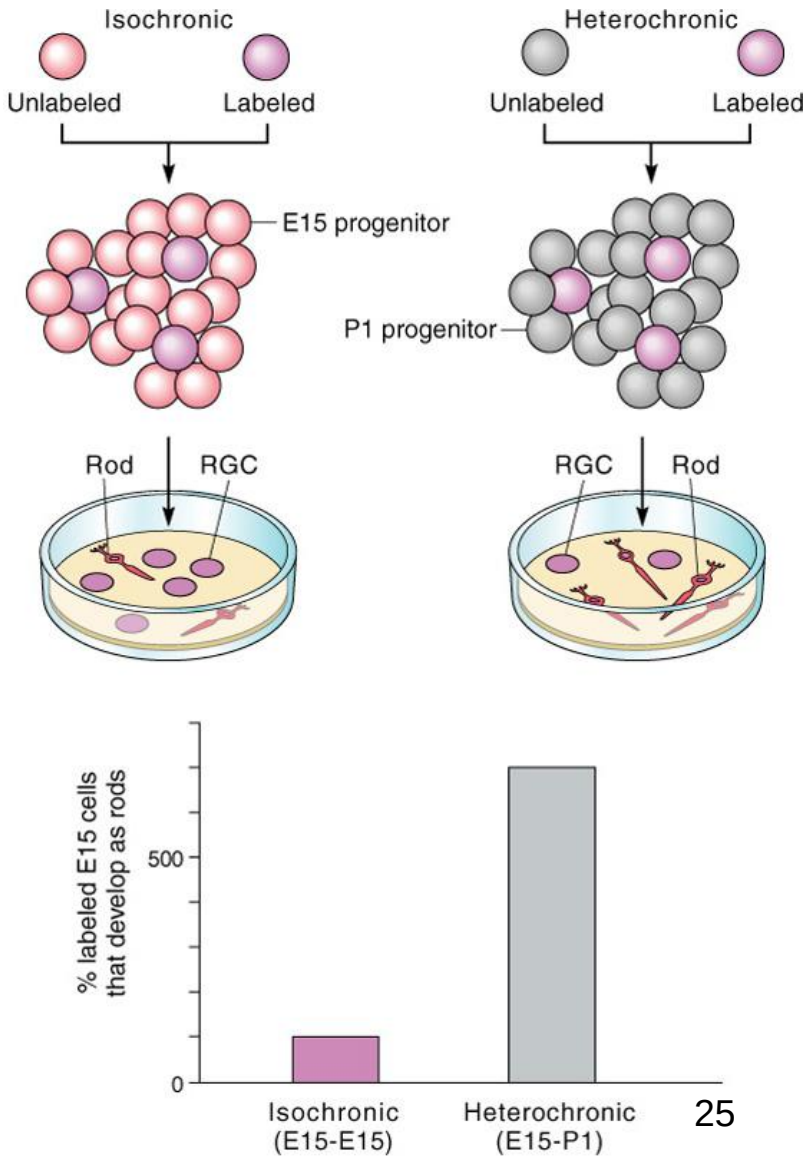
The Journal of Comparative Neurology
Volume 474, Issue 2, pages 304-324, 20 MAY 2004 DOI: 10.1002/cne.20134
http://onlinelibrary.wiley.com/doi/10.1002/cne.20134/full#fig7

Differentiating cells repress production of more of the same cell type and/or promote production of other cell types.

The retinal ganglion cell is the first cell type generated in the retina, and they promote development of later cell types.

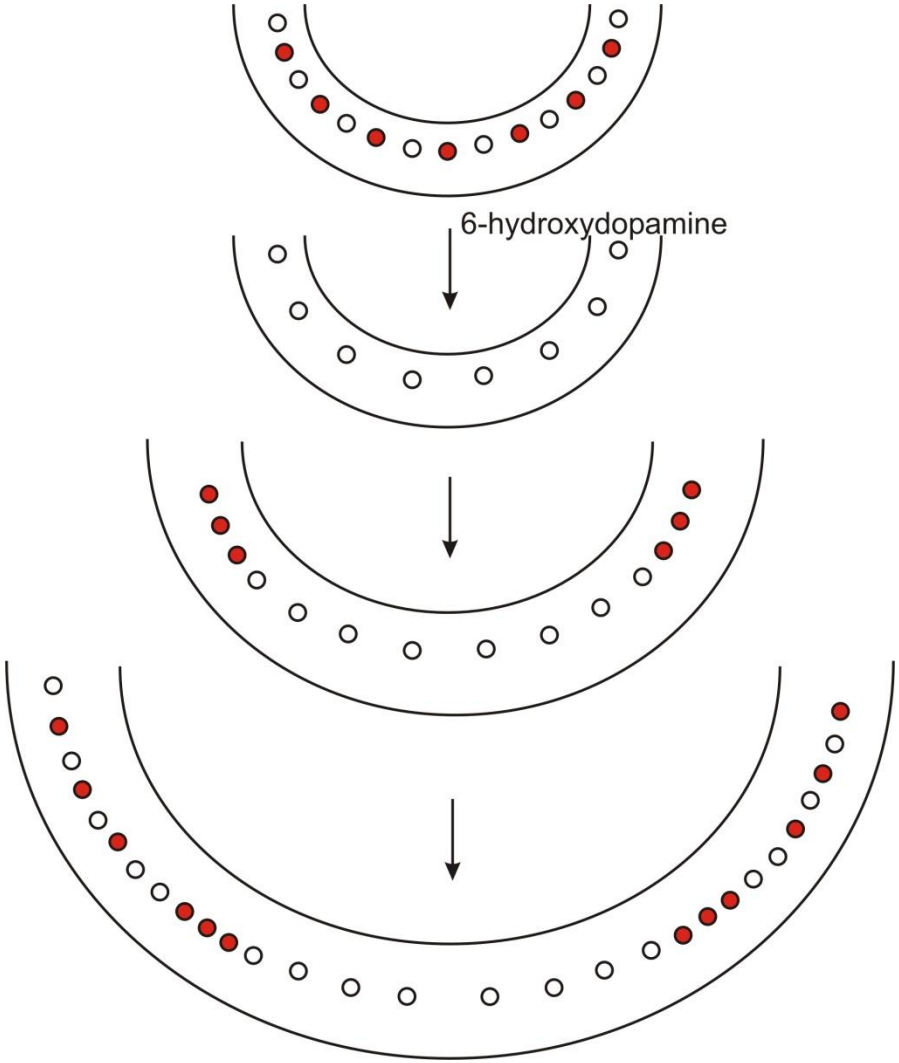
- Co-culturing older retinal cells that included ganglion cells with younger retinal cells without ganglion cells reduced ganglion cell production and increased rod cell production in the younger progenitor cell population.

- Eliminating the ganglion cells in the older retina abolished the effect.



Differentiating cells repress production of more of the same cell type and/or promote production of other cell types.

- Elimination of dopaminergic cells in retina increased subsequent development of dopaminergic cells.



Differentiating cells repress production of more of the same cell type and/or promote production of other cell types.

- Elimination of crest cells that would normally differentiate into dorsal root ganglion (DRG) neurons resulted in later developing cells becoming DRG neurons.

Newly differentiating cells secrete factors that change the competence of neighboring progenitor cells.

Differentiating retinal ganglion cells promote generation of later born retinal cell types:

- Newly differentiating retinal ganglion cells secrete VEGF, Sonic Hedgehog (Shh) and the TGFβ family member GDF11, all of which have been linked to repressing further ganglion cell production and promoting generation of later cell types.

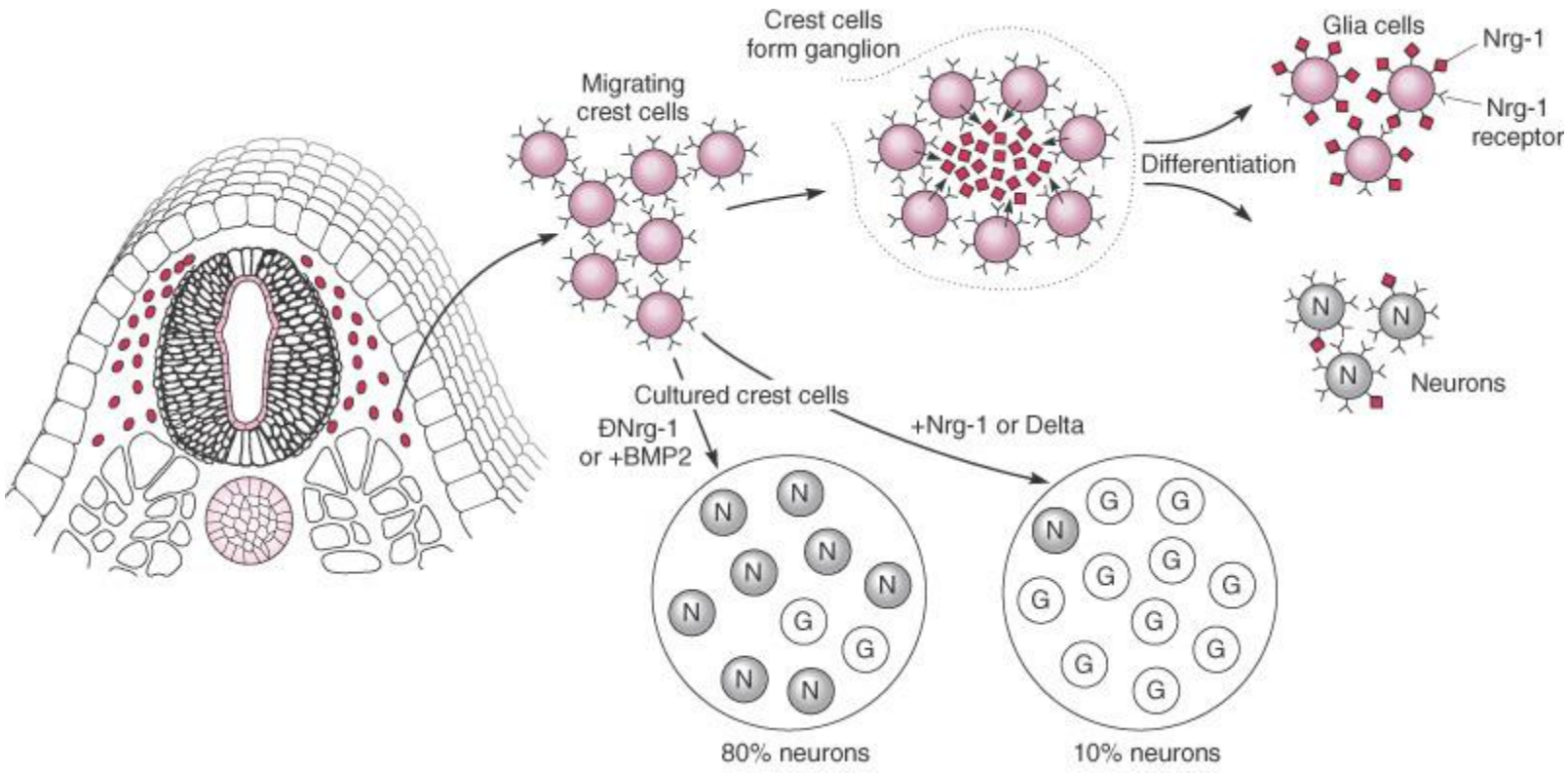
Newly differentiating cells secrete factors that change the competence of neighboring progenitor cells.

Differentiating dorsal root ganglion neurons promote generation of glial cells:

- Dorsal root ganglion (DRG) neurons develop from neural crest.
- Glial cells develop from neural crest after the neurons.
- As crest cells finish migration, aggregate as a ganglion and begin to differentiate as neurons, they secrete Neuregulin-1 (Nrg-1).
- Migrating crest cells express the receptor for Nrg-1.

Newly differentiating cells secrete factors that change the competence of neighboring progenitor cells.

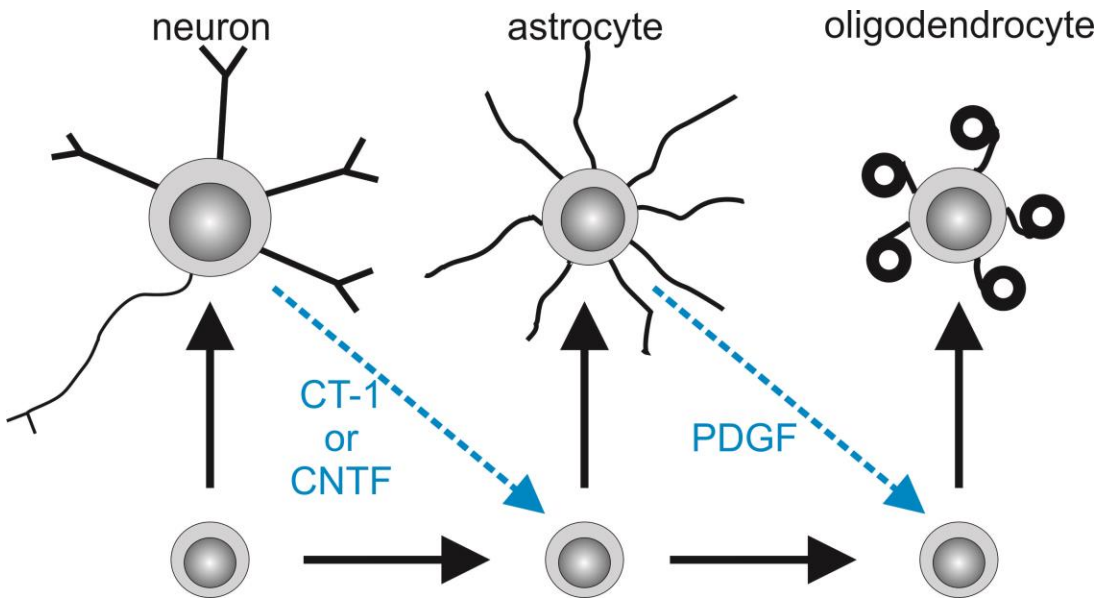
- Crest cells in culture develop into neurons and glia.
- With Nrg-1 added to the medium, they all become glia.
- Blocking expression of Nrg-1 in the cultured cells caused them all to become neurons.



Newly differentiating cells secrete factors that change the competence of neighboring progenitor cells.

In cultures of cortical progenitor cells:

- The cytokines Cardiotrophin-1 (CT-1) or ciliary neurotrophic factor (CNTF) terminate neurogenesis and promote astrocyte genesis.
- PDGF promotes oligodendrocyte genesis.

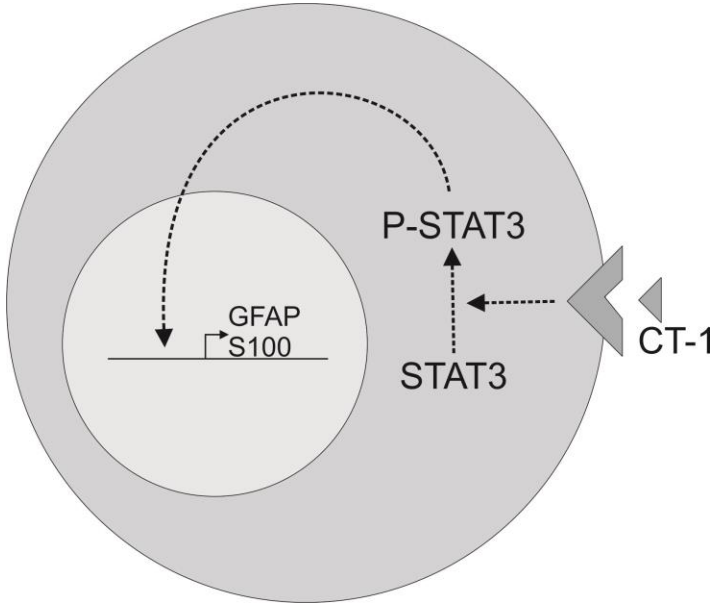


Newly differentiating cells secrete factors that change the competence of neighboring progenitor cells.

- Differentiating neurons in cortex express and secrete cardiotrophin-1 and CNTF.

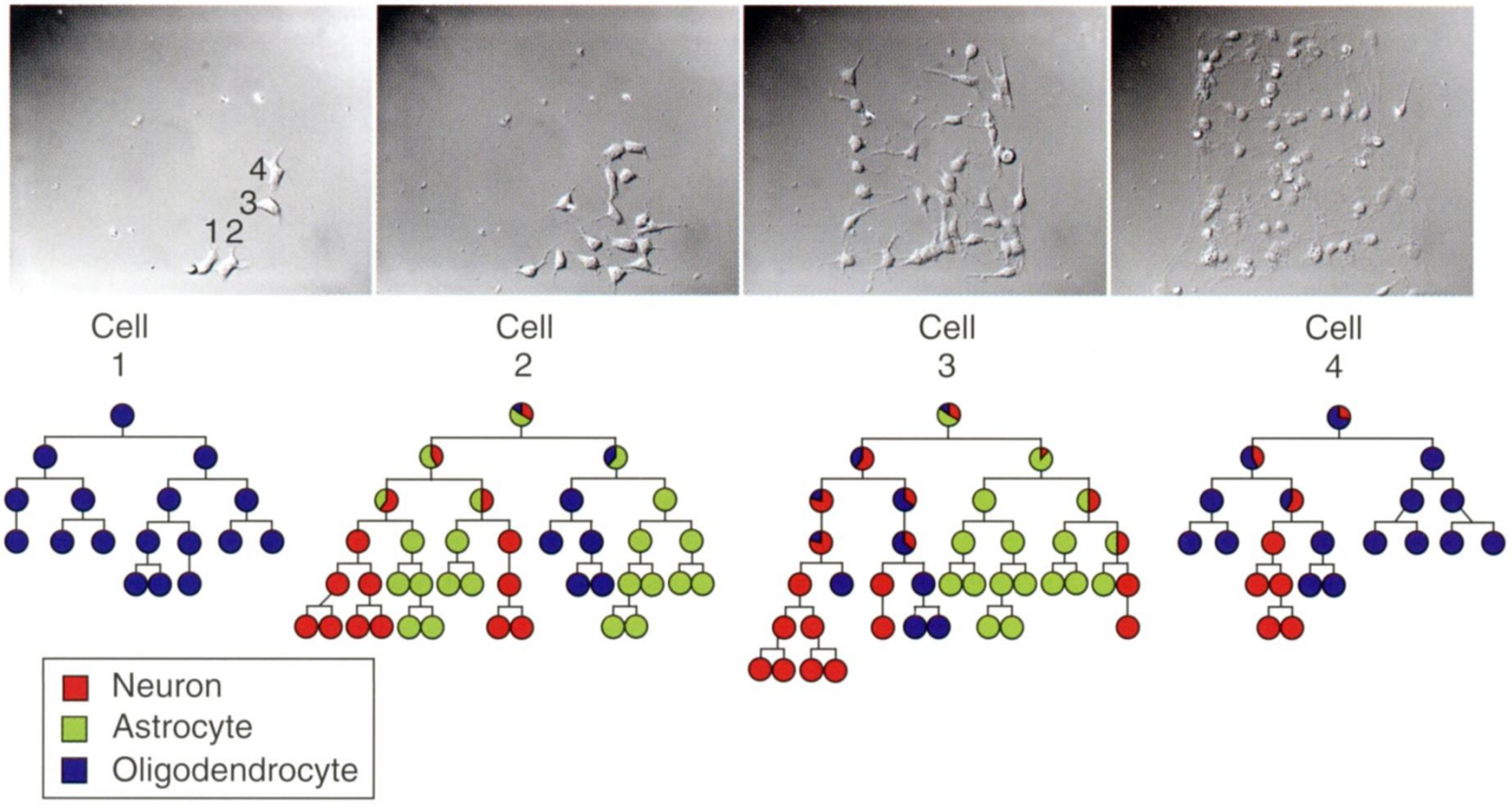
Newly differentiating cells secrete factors that change the competence of neighboring progenitor cells.

- CT-1 and CNTF act via cell surface receptors to activate STAT3 by phosphorylation.
- Active STAT3 binds the promoter of astrocyte specific proteins including GFAP and S100.
- In early development, the STAT3 binding sites in the promoters of these genes are methylated, so STAT cannot bind and only neurons are generated.
- Notch activation demethylates these STAT binding sites.



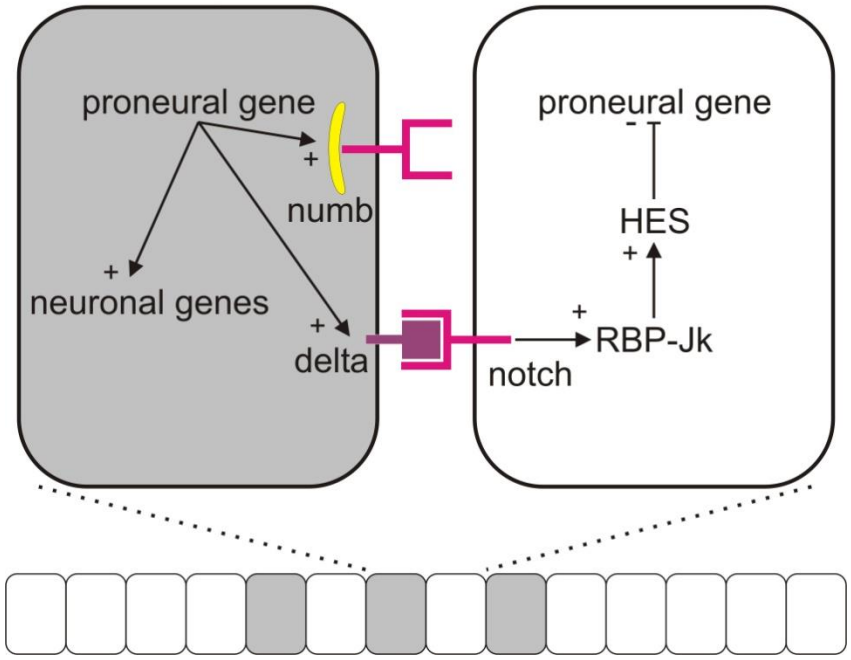
Newly differentiating cells secrete factors that change the competence of neighboring progenitor cells.

- The lineage relationship of neuron to astrocyte to oligodendrocyte is not an invariant sequence.



Notch signaling can promote production of later cell types.

- Progenitor cells express the cell surface receptor, Notch.
- Newly differentiating neurons, including retinal ganglion cells express the Notch ligand, Delta.
- Blocking Notch signaling in the developing retina increased ganglion cell production.
- Constitutive activation of Notch repressed ganglion cell production.
- Thus, new ganglion cells may change the competence of progenitor cells by activation of Notch.
- Similar results have been obtained for tissues other than retina.



Thus, newly differentiating cells effect a change in the competence of neighboring progenitor cells.

- As one cell type begins to differentiate, it acts on neighboring progenitor cells through a variety of signaling mechanisms to repress further production of that cell type and/or to promote production of the next cell type.