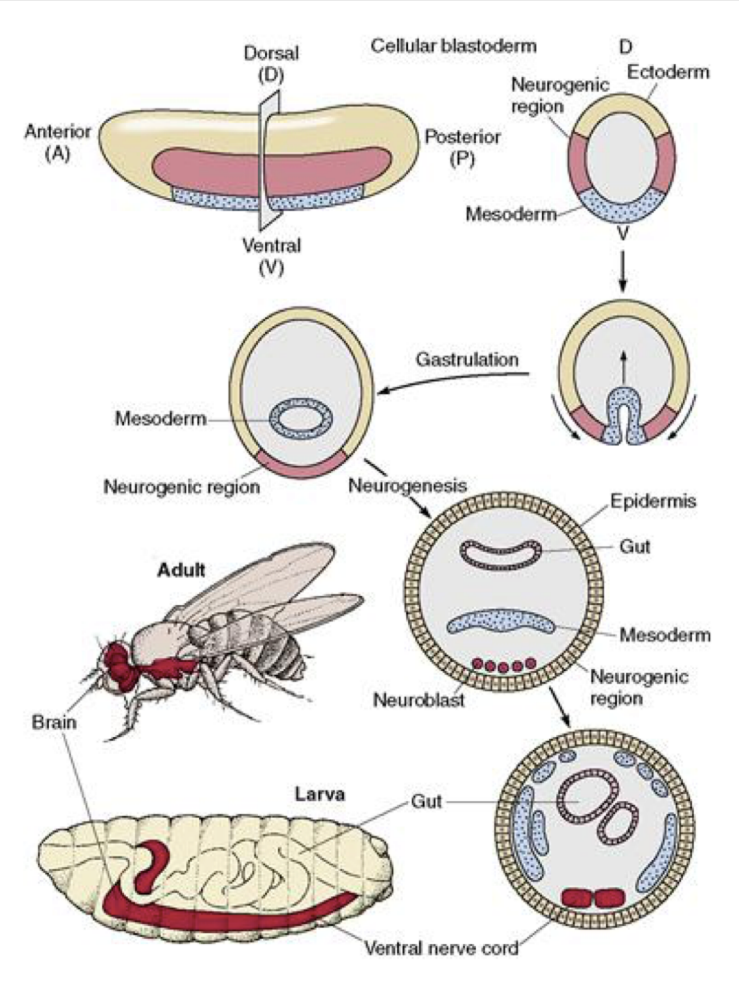
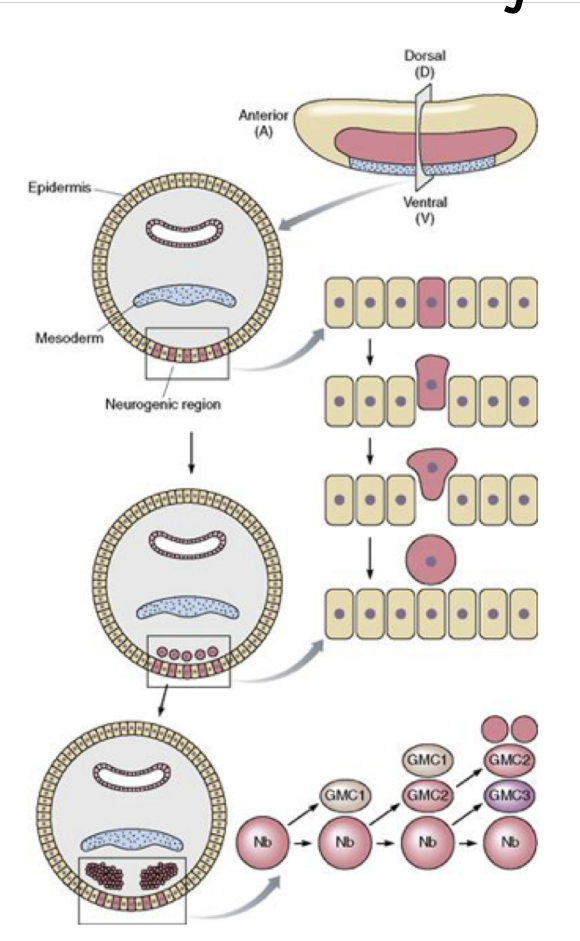
Early steps in Drosophila Neurogenesis

start@unito



- Most of the nervous system in Drosophila derives from the ventro-lateral part of the cellular blastoderm
- Following gastrulation, the neurogenic region (ectoderm) is at the ventral midline→ it will give rise to the ventral nerve cord (CNS)
- More anteriorly, the procephalic neurogenic region gives rise to the cerebral ganglia

Early steps in neural development in Drosophila

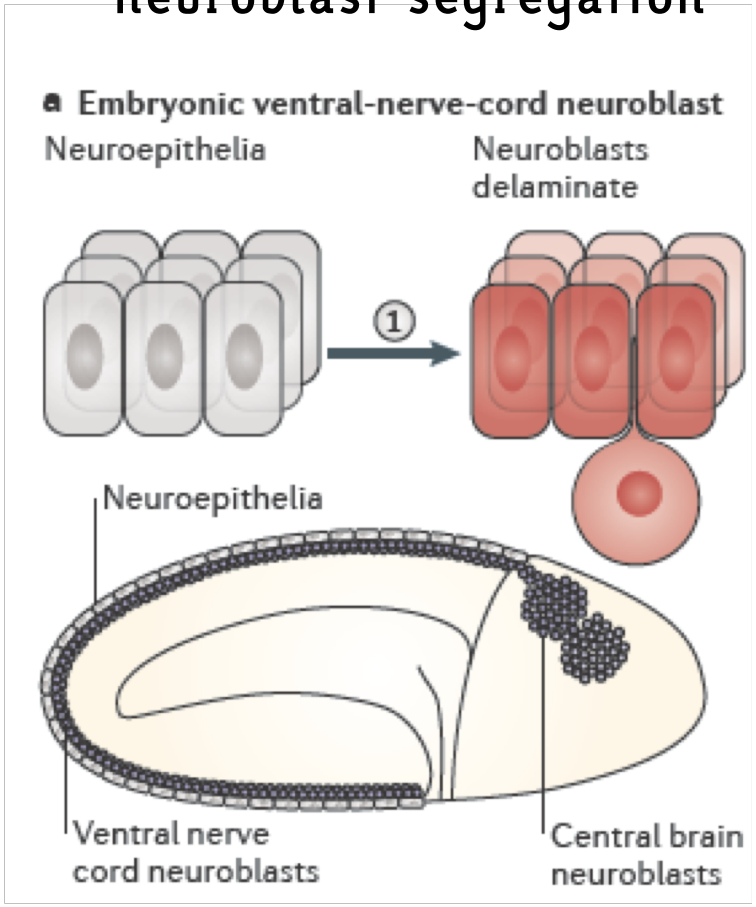


1. Neurogenic region established by Dpp inhibition through sog

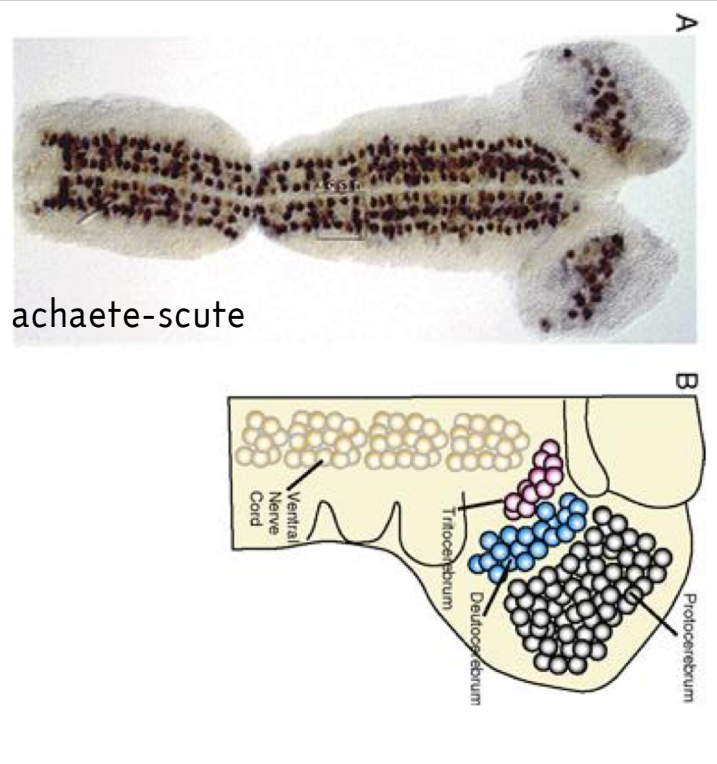
2. **Delamination**: single cells separate from the neurogenic ectoderm by delamination in several waves and move into the interior of the embryo to form neural precursor cells called **Neuroblasts** (Nb)

3. Once inside the embryo the Neuroblasts undergo a stereotyped pattern of asymmetric divisions giving rise to **ganglion mother cells** (GMCs) that in turn originate neurons or glia

Interactions among the ectodermal cells in controlling neuroblast segregation



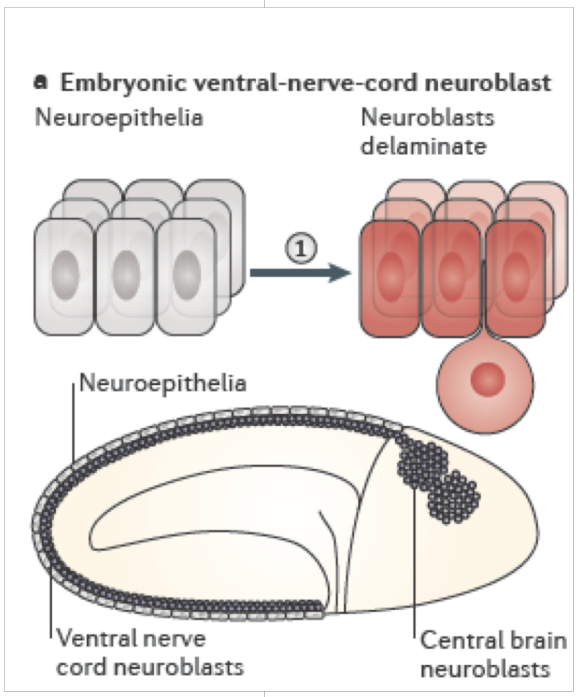
Proneural clusters

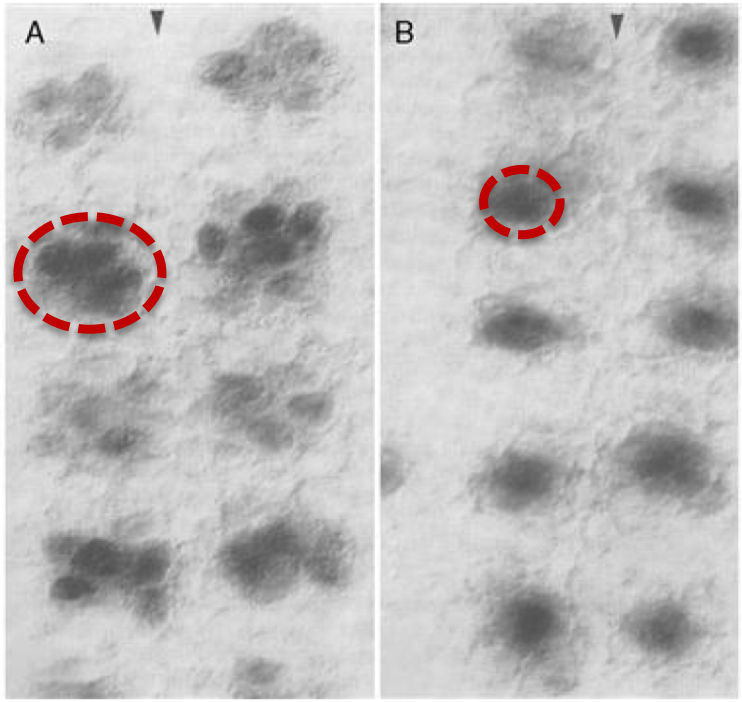


Ventral view of a Drosophila embryo

Stereotyped pattern:

The neuroblast that delaminate in a specific position gives rise to the same neurons and glia in each segment





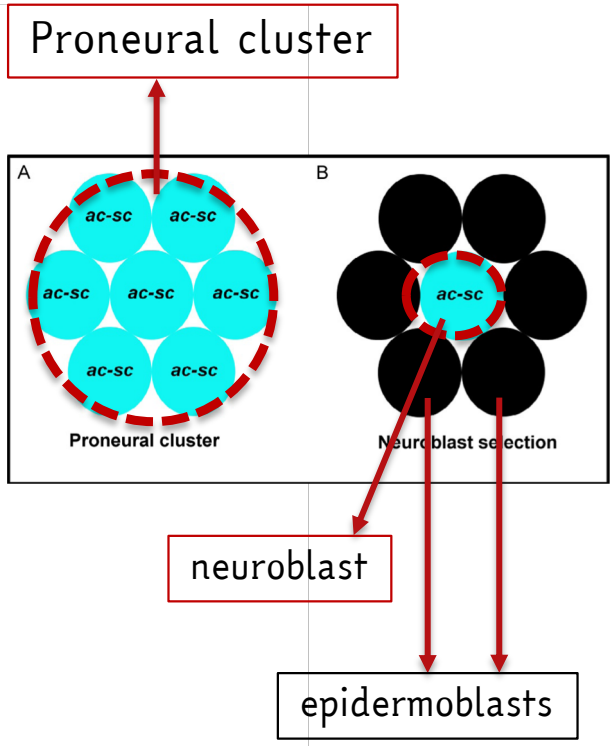
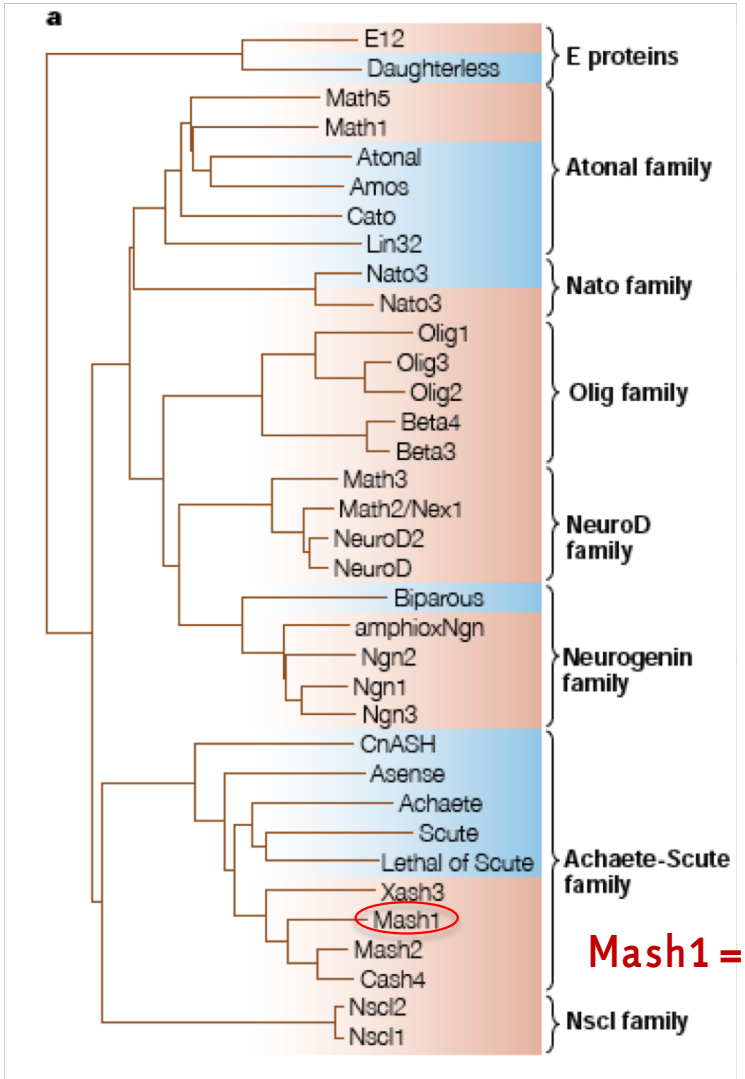
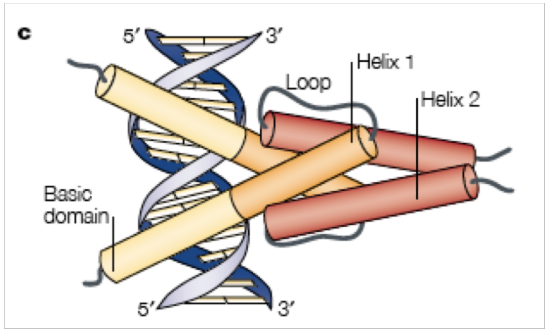


Fig. 1.23 Neuroblast segregation in the *Drosophila* neurogenic region proceeds in a highly patterned array. A. In this embryo stained with an antibody against *achaete-scute (as-c)* protein, clusters of proneural cells in the ectoderm express the gene prior to delamination. B. A single neuroblast develops from each cluster and continues to express the gene. The other proneural cells downregulate the *as-c* gene.(From Doe, 1992)

Dendrogram of the sequence of the basic helix-loop-helix domain of invertebrate (blue) and vertebrate (red)



Proneural genes
key regulators of neurogenesis

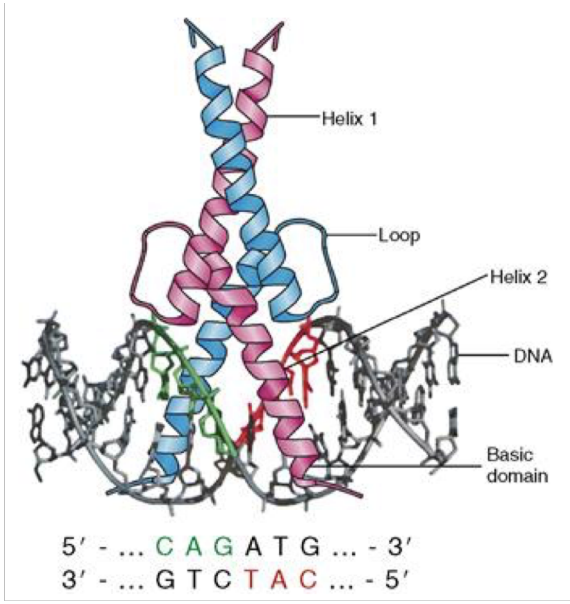


Proneural proteins bind E-box (CANNTG) DNA sequences as heterodimeric complexes formed with ubiquitously expressed bHLH proteins (E proteins)

Activate trascription
of neuronal genes

Mash1 = mammalian achaete scute homolog-1 (Ascl1)

Proneural genes
key regulators of neurogenesis



Multifaceted role in neural development

- generic neural fate
- Specification of subtype identities

Neuroblasts are specified by cell interactions

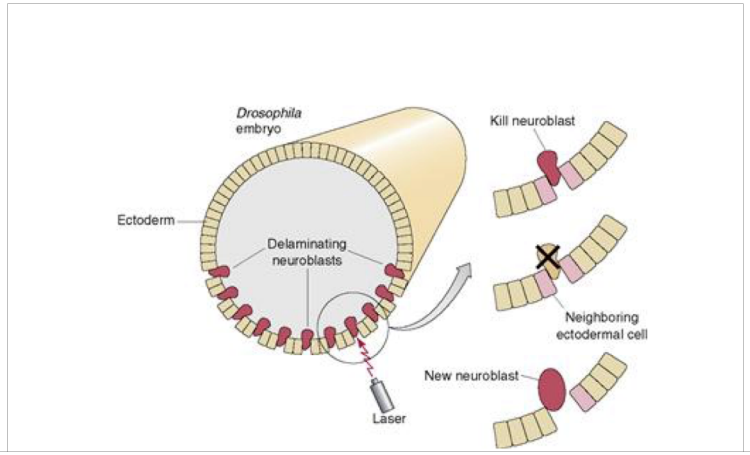


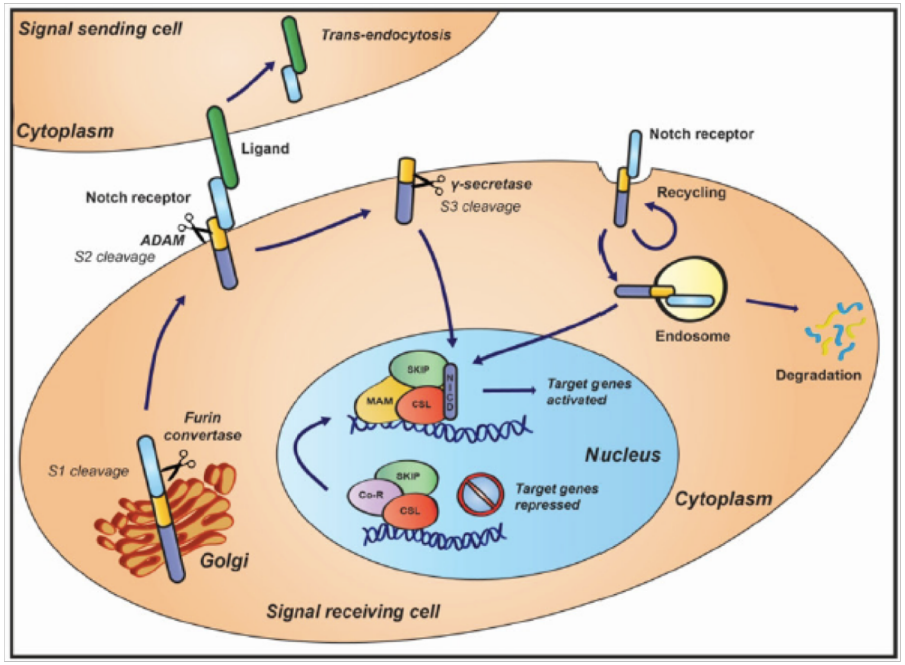
Fig. 1.26 Ablation of the delaminating neuroblast with a laser microbeam directed to the ventral neurogenic region of the fly embryo causes a neighboring ectodermal cell to take its place. This experiment shows that the neuroblast inhibits neighboring cells from adopting the same fate via the mechanism of lateral inhibition.

Notch pathway

The developmental logic of **Notch:**

Notch signaling **couples cell fate acquisition by an individual cell to the cell fate choices made by its "next door neighbours"**

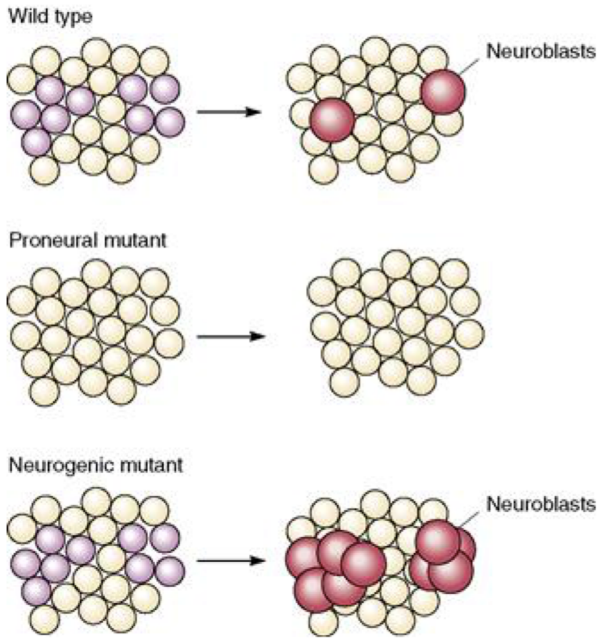
Lineage segregation
by lateral inhibition



Carrieri and Dale, Front. Cell Dev. Biol. (2017)

Proneural genes

Neurogenic genes



Embryos lacking the proneural genes *achaete/scute* or *lethal of scute* have a reduced number of neuroblasts

Notch/Delta mutants produce a remarkable excess of neurons at the expense of epidermis

Fig. 1.24 Neurogenic genes and proneural genes were first identified in the *Drosophila* due to their effects on neural development. In the wild-type embryo (top), only one neuroblast (red) delaminates from a given proneural cluster in the ectoderm. However, in flies mutant for proneural genes (middle), like *achaete scute*, no neuroblasts form. By contrast, in flies mutant for neurogenic genes (bottom), like *notch* and *delta*, many neuroblasts delaminate at the positions where only a single neuroblast develops in the wild-type animal. Thus, too many neurons delaminate—hence the name "neurogenic."

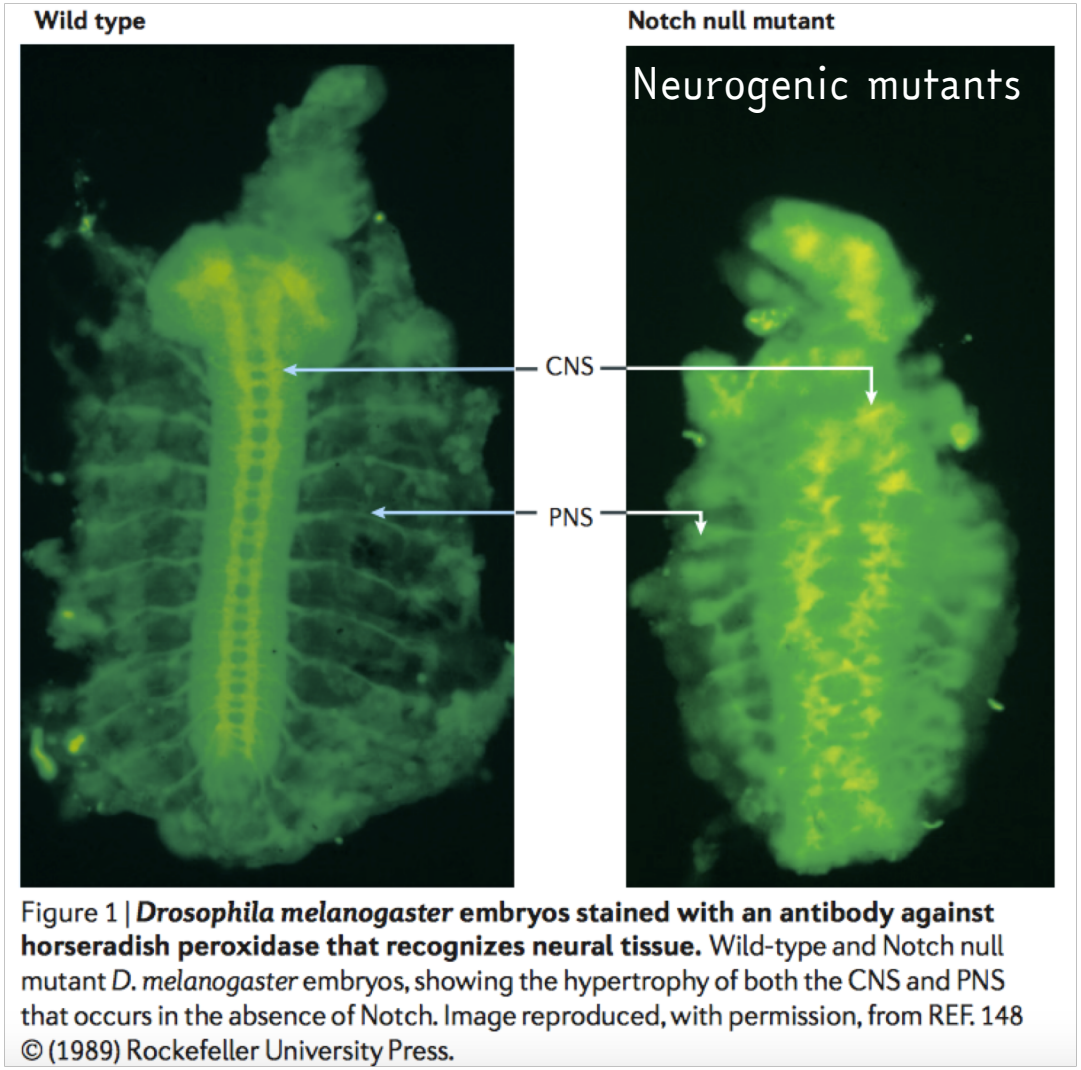
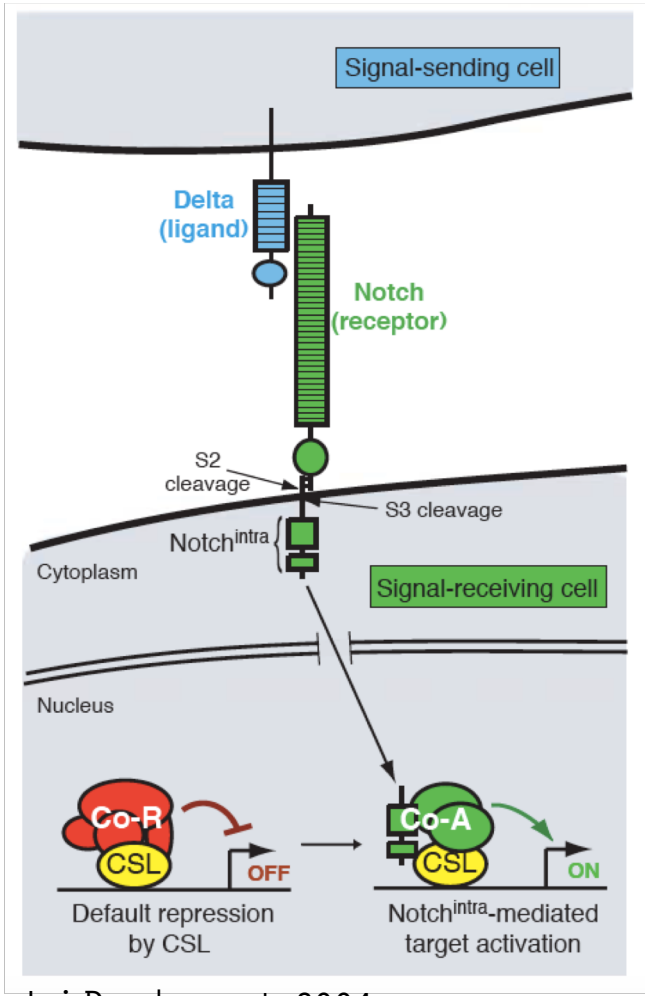


Figure 1 | ***Drosophila melanogaster* embryos stained with an antibody against horseradish peroxidase that recognizes neural tissue.** Wild-type and Notch null mutant *D. melanogaster* embryos, showing the hypertrophy of both the CNS and PNS that occurs in the absence of Notch. Image reproduced, with permission, from REF. 148 © (1989) Rockefeller University Press.

Neurogenic genes

- Describe a loss-of-function condition
- Do not function exclusively during neurogenesis



Lai Development, 2004

Basic mechanism of the Notch pathway

The key players are:

- **Delta-type (ligand9**
- **Notch (receptor)**
- **CSL (TF)**

Activation of Notch by its ligand triggers two proteolytic cleavages of Notch: S3 cleavage (by a protease gamma-secretase) releases the Notch intracellular domain (Notch-ICD) which translocates to the nucleus and activates CSL.

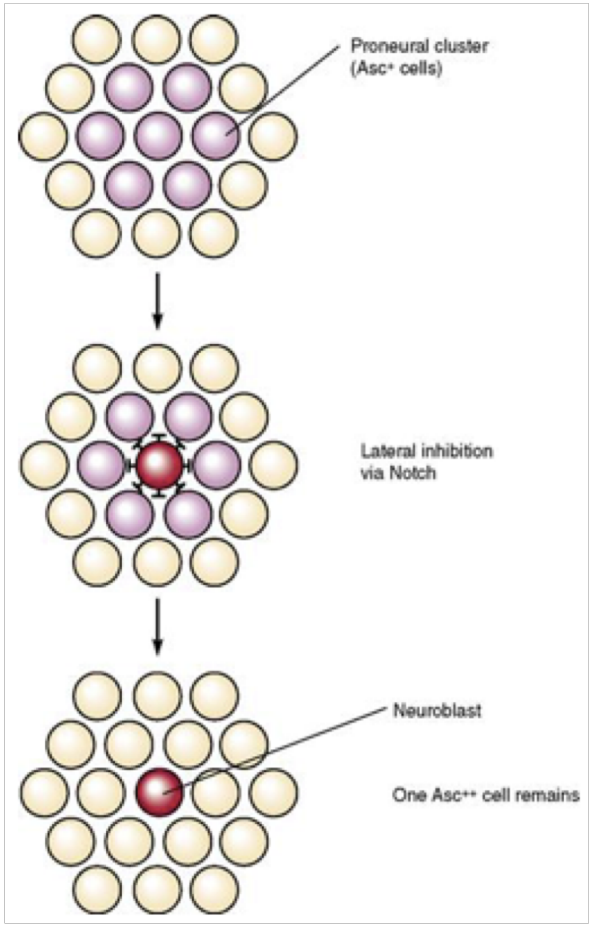
→ In the absence of nuclear Notch-ICD, CSL associates with a co-repressor complex (Co-R), which actively represses the transcription of Notch target genes.

→ The CSL co-repressor complex is displaced by a co-activator complex containing Notch ICD.

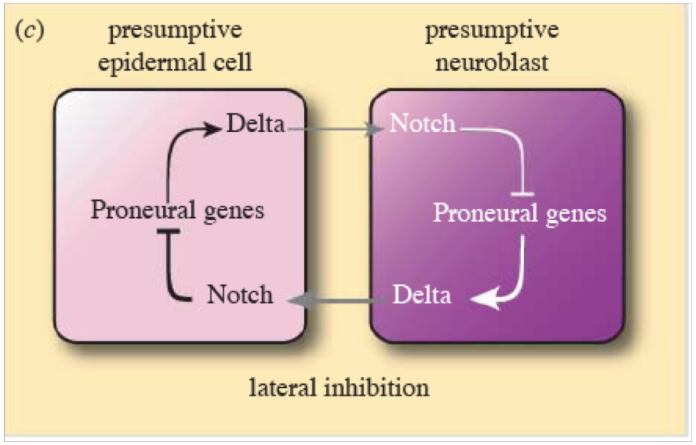
CSL (CBF1, Suppressor of Hairless, Lag-1)

Table 1. Names of core components of Notch signaling (ligand, receptor and transcription factor) in different species

Core component	*C. elegans*	*D. melanogaster*	Mammals
Ligand	LAG-2 APX-1 ARG-2 F16B12.2	Delta Serrate	Delta-like1 (DLL1) Delta-like2 (DLL2) Delta-like3 (DLL3) Jagged 1 (JAG1) Jagged 2 (JAG2)
Receptor (Notch)	LIN-12 GLP-1	Notch	Notch1 Notch2 Notch3 Notch4
Transcription factor (CSL)	LAG-1	Suppressor of Hairless [Su(H)]	CBF1/RBPJκ RBPL



Key to the process of **lateral inhibition** in *Drosophila* is the direct and dose-dependent transcriptional **activation of the Notch receptor ligand Delta** by proneural genes

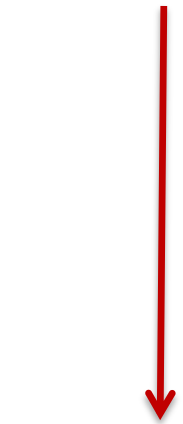


Low Notch activity→ neural fate
High Notch activity→ epidermal fate

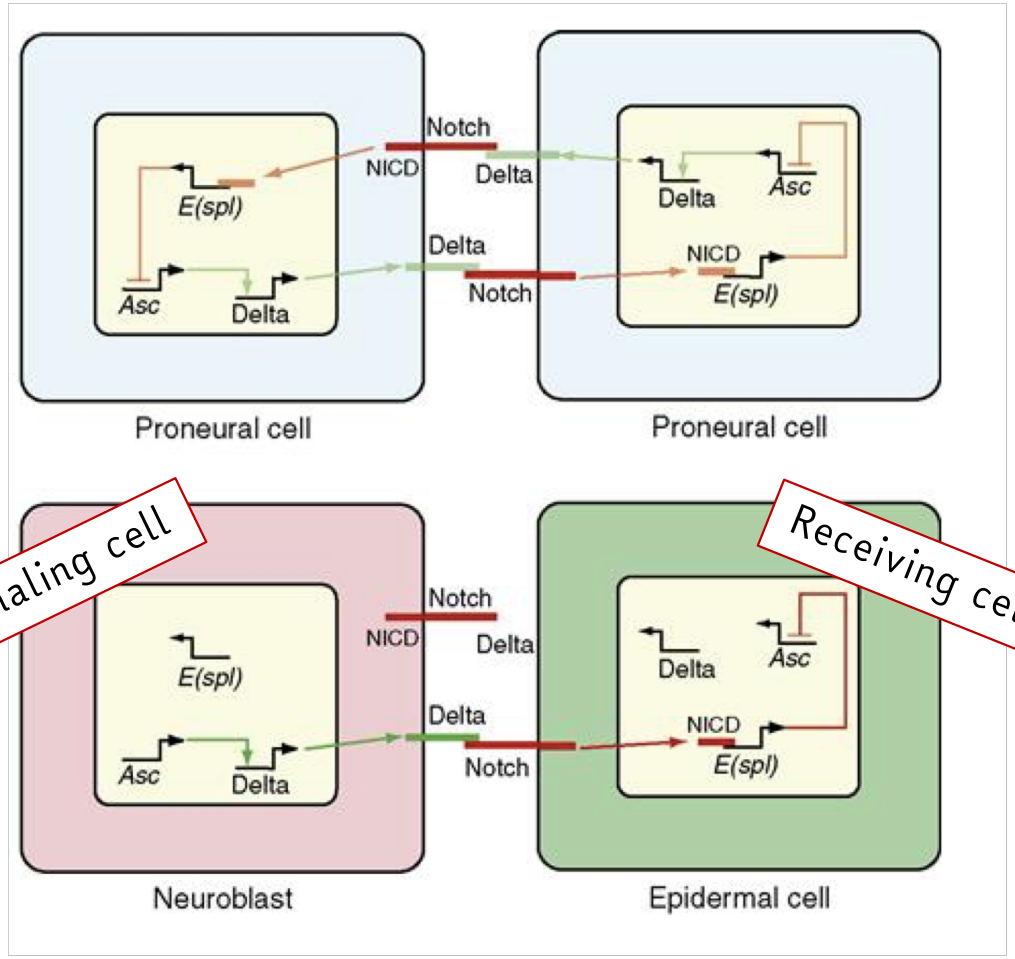
→ *The cell that initially has higher levels of proneural genes or Delta expression (or lower levels of Notch expression) will become a neuroblast*

Lateral inhibition and Notch/Delta pathway

2 equivalent cells

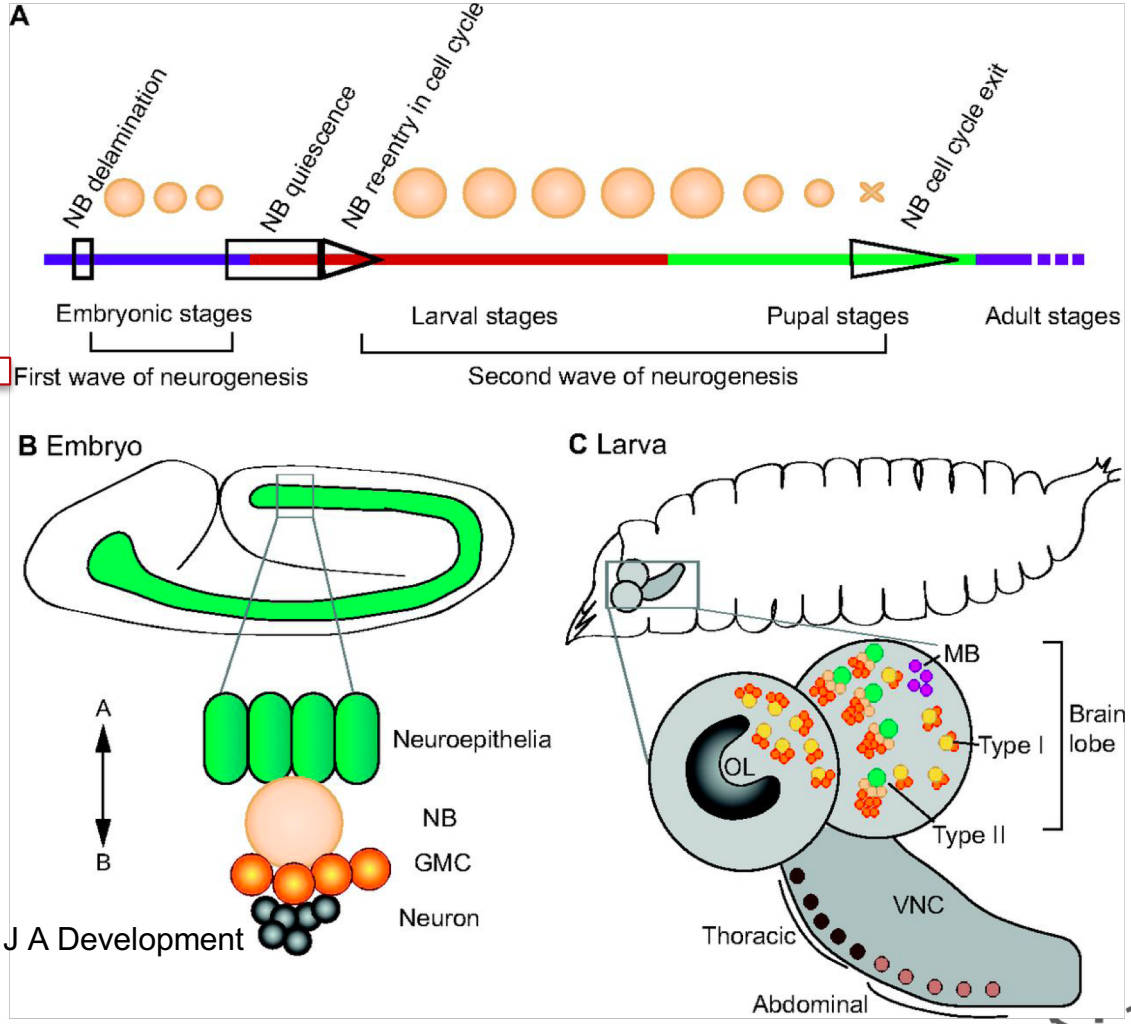


not equivalent



Neurogenesis in Drosophila

10% adult neurons



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