Chapter 3

Genesis and Migration

Functional homologies between neurogenic genes:
Neurogenic gene sog (~chordin) inhibits dpp (~BMP) signaling

Fig. 1.19
Proneural genes experience Notch-Delta Lateral Inhibition

Notch/Delta interaction blocks neural fate in neighboring cells by blocking Asc via Hes.

C. elegans
- Constant cell number (eutely)
- Lineage-dependent

Fig. 1.28

Fig. 1.29

Fig. 1.3
Drosophila:
• Stereotyped pattern of neurogenesis
• Lineage-dependent

Retroviral labeling technique
Proliferation in a pseudostratified epithelium

Vertebrates:
• Fate and position are less predictable
• Clonal analysis reveals indeterminate fates of daughter cells
Birthdating studies:
- 3H-Thy incorporates into DNA in S phase
- It is available for ~2 hrs
- It is diluted by further cell divisions
- It can be detected with autoradiography
- It can tell us where neurons came from before migration
- It can tell us when neurons were “born”
- What does it NOT tell us?

Fig. 3.3

Proneural genes experience Notch-Delta Lateral Inhibition

Notch/Delta interaction blocks neural fate in neighboring cells by blocking Asc via the E(spl) member Hes-1.
The cell cycle elongates with age

Fig 3.4

Neuroblast or terminal fate?
Assay by Q fraction msmt

Green = Nb
Red = Neuron

Early
Expansion phase
(low Q fraction)

Late
Neurogenic phase
(high Q fraction)

Terminal fate

Fig 3.5
Cell cycle control

- G1 to S phase (cyclinD/Cdk4) is well-controlled
- Cyclin binding to Cdns activates Cdns
- Cdns phosphorylate key proteins that push each next step
- Cdk Inhibitors p21 and p27 cause exit from cell cycle
- Rb is a tumor-suppressor protein that when active binds E2F1
- Rb is phosphorylated and inactivated by cyclinD/Cdk4
- Rb mutation (loss) frees E2F1 to push past the G1 to S restriction point of the cycle, possibly leading to tumor formation.

Fig 3.6

When hypophosphorylated, Rb associates with E2F, stopping it from acting as a transcription factor.

Phosphorylation of Rb allows for E2F to dissociate from it and carry out its function. E2F is a transcription factor which drives the expression of genes involved in DNA synthesis and cellular growth.

When the cell is ready to begin replicating its DNA, Rb is phosphorylated by the action of various cyclins and cyclin-dependent kinases.

Modified from Cules, Nature Reviews Molecular Biology 6, 647-659, http://www.nature.com/nrm/journal/v6/6a/full/nrm2233-f2.jpg
Manipulating cell cycle genes in cerebral cortex

In vitro studies of proliferation show progressive restriction of fate

Multipotent progenitors are indeterminant in vitro and in vivo
Proneural genes and the Notch pathway

- Hes-1, Notch promote progenitor fate
- Hes-1 expression self-inhibits: oscillates in antiphase with proneural factors
- Proneural transcription factors promote expression of Notch ligands such as Delta
- Any slight imbalance in Notch ligand expression is amplified, leading to neural fate and suppression of neural fate in neighbors

Fig 3.10

Notch-Delta signaling

Fig. 1.28
Fig. 1.24

Wild type

Proneural mutant (no proneural gene Asc, so no neuroblasts)

Neurogenic mutant (no neurogenic genes Notch/Delta, so no lateral inhibition)

Fig 3.9

Mitogens and GFs influence proliferation/fate

Gliogenesis

Astrocyte

FGFs

FGFR

Trk

Neurotrophins

Pro-neural bHLH TFs

Id1/3

Hes5

Neuron

Responsiveness to these signals can vary over time due to epigenetic modifications of their promoters

Neurogenesis

Neurogenesis

Glia

GFAP

S100

EGFR

CNTFR

NF1

Smad

Suh

Notch

Delta
Oligodendrocyte development

Molecular switches alter fate
Note: Glial progenitors can produce neurons or glia

Neurogenesis in tadpole and adult frog retina

Fig 3.11

Fig 3.20
Adult Neurogenesis in Olfactory Bulb

Fig 3.21

Adult Neurogenesis in Mouse Hippocampus
Are new neurons functional?

Fig 3.22
Cortical cytoarchitecture

Fig 3.12

^3H-thymidine birthdating technique

A

\[ ^3H \text{-thymidine} \]

Pregnant female

B

\[ ^3H \text{-Thymidine} \]

Fig 3.3
Birthdating studies: Cortical Histogenesis-Making layers in an inside-out sequence of neurogenesis and migration

Cortical Histogenesis: Making layers (monkeys)
Cortical Histogenesis

3 stages:
1. Preplate formation
   1. Cajal-Retzius cells
   2. Subplate cells
2. Cortical plate splits the preplate
3. Formation of 6 layers in an inside-out order

Radial glia (IPCs) guide migration and generate neurons

Fig 3.13

Fig 3.14
Genesis and Migration of Cortical GABA Neurons

A. Culturing cerebral cortex without ventral telencephalon almost eliminates GABAergic neurons from cortex. B. Labeling a small population of precursor cells in LGE and following their migratory path and fate shows that they migrate dorsally and contain GABA.

2nd edition Fig 3.20 Origin of Cortical Inhibitory (GABAergic) neurons.
A. Culturing cerebral cortex without ventral telencephalon almost eliminates GABAergic neurons from cortex. B. Labeling a small population of precursor cells in LGE and following their migratory path and fate shows that they migrate dorsally and contain GABA.
Cerebellar Histogenesis

Fig 3.16

Fig 3.17
A-C. Cerebellar Purkinje neurons produce Shh (A-red, B-blue), which is detected by receptors ptc and smo in the granule cell neurons (A-blue, C-brown), promoting the proliferation of matching numbers of granule cell neurons.

D. Sonic hedgehog stimulates progenitor proliferation in cerebellum, cerebral cortex, and tectum.

Reelin Function

Fig 3.18
Reelin Function

Fig 3.19

Neural Crest Migration

Fig 3.23
Chick-quail chimera method of Nicole LeDouarin