

LECTURE 35 NEUROGENESIS & NEURAL STEM CELLS

From Chapt. 21, p. 1204-1210

Figures: 21-11, 21-48, 21-57 to 21-62, 21-64, 21-95.

- 1) Segmentation & homeotic genes define compartments/segments, control expression of subsequent genes that regulate finer, local details
- 2) **Cell differentiation is foreshadowed by localized expression of specific classes of gene regulatory proteins**
 - **Example, Fig. 21-58:** expression of *scute* or *achaete* ("proneural" genes encoding bHLH TFs) forecasts where precursor cells (**sensory mother cells**) for **bristles** will form in *Drosophila*
- 3) **Local interactions among cells via Notch signaling**, together with asymmetric divisions, direct individual cells to follow diff't, complementary paths of terminal diff'n

EXAMPLE: *Drosophila* mechanosensory bristles (Fig. 21-57): example of local specification of cell fate by "lateral inhibition" (Fig. 21-11)

- Adult fly body (incl. thorax, wings, legs) covered w/ bristles; many are mechanosensory (touch sensitive)
- Each m. bristle develops from **single sensory mother cell (s.m.c.)**
- Each s.m.c. is selected from ectoderm by **lateral inhibition via Notch/Delta signaling pathway:**
 - **Notch:** transmembrane receptor
 - **Delta:** transmembrane ligand for Notch
 - **Achaete-Scute family TF's activate expression of Delta** in proneural cell group; initially the cells also all express Notch
 - **Fig. 21-59: Binding of Delta to Notch sends NEGATIVE SIGNAL into the Notch-expressing cells**
 - Delta binding activates **cleavage of Notch & nuclear localiz'n of Notch-intracellular domain (NICD)**
 - **Notch^{ICD}** is transc. cofactor, binds **Su(H)**, a DNA binding TF, switches Su(H) from repressor to activator: **Notch^{ICD}/Su(H)** activates "Notch target genes", including *Enhancer of Split Complex* genes [*E(Spl)C*] encoding other bHLH TFs that **repress transc. of *achaete-scute* family genes**
 - future s.m.c. expresses slightly more Delta, it's competitive edge is amplified by feedback mech: higher Notch signaling in surrounding cells depresses their Achaete-scute & Delta express'n, blocking *their* neural fate potential (**hence, "lateral inhibition"**) (surrounding cells differentiate into epidermis)
- **Fig. 21-60:** when lateral inhibition is switched off by **reducing Delta**, **multiple s.m.c.'s form: excess bristles develop** (if Delta lacking completely, external bristle parts don't form)
 - How was Delta reduced in limited region of the thorax in exp't shown in Fig. 21-60? **By FLP/FRT-mediated somatic recombination (Fig. 21-48)** to create *Delta*^{-/-} patch of cells during development of *Delta*^{+/-} fly
- **S.m.c. goes on to produce lineage of 5 cells (Fig. 21-57)**
 - Diff't fates of cells in s.m.c. lineage also requires Notch signaling; **Fig. 21-61:** diff't fates depend on **asymmetric inheritance of Numb**, membrane protein causing cell autonomous degrad'n of

Notch^{ICD} (daughters inheriting Numb can't respond to Delta)

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- **Neurogenesis in vertebrates:**
 - as in flies, proneural genes homologous to *achaete-scute* are required; Notch signaling also required; nascent neurons express Delta
 - **Fig. 21-64:** Blocking Notch signaling w/ dominant negative truncated Delta causes excess neurons to form in frog embryo.
 - **In the vertebrate cerebral cortex (Fig. 21-95):**
 - new-born neurons migrate through layers of older neurons, out to newest (outermost) layer (c.c. develops "inside-out")
 - neural stem cells located at inner layer in cortical region; undergo mitosis here; Notch & Numb noted to become localized basally in these cells
 - if stem cell divides horizontally, both daughters get Numb/Notch, remain stem cells.
 - if stem cell divides vertically, the basal daughter loses its apical attachment & gets all the Numb/Notch, becomes post-mitotic, commits to differentiate, migrates away.
- Notch signaling is important for fine-grained patterning of diff't cell types in many (if not all!) tissues; regulates spacing, proper nrs. of diff't cell types, diversity of types. Mutations in Notch signaling components upset balance of cell types
- Final different'n steps require addit'l developmental regulators for specific cell fates (eg. MyoD & related bHLH TFs for muscle cells)