Developmental Neuroscience January 24, 2008

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Neural Patterning I - Where does the *Drosophila* nervous system come from and how is neural fate specified?

Questions/issues to keep in mind as we progress:
Is there neural induction? from mesoderm? via morphogen gradients within the ectoderm?

Drosophila NBs as neural stem cells with limited lifetimes. Why don't they divide indefinitely? Could they be caused to?

1) The *Drosophila* life cycle
Embryogenesis and the formation of germ layers (~24 hrs)
Larval life (3 instars, ~96 hrs total)
Pupation (5-6 days) - and CNS remodeling
Adulthood (weeks)

2) Dorsoventral patterning in *Drosophila*
Maternal contributions
Zygotic realization via the BMP pathway
Parallels (inverted) to vertebrate development

3) Anteroposterior patterning in *Drosophila*
Maternal contributions
Zygotic realization

4) Now that we know where the neurogenic ectoderm is, what happens next?
Activation of proneural gene expression in clusters (AS-C complex) *
Restriction of AS-C expression to single cells (NBs) *
Delamination of NBs
Asymmetric cell division gives rise to another NB + GMC
(typically happens ~8x/NB)
GMCs divide, usually symmetrically to give rise to 2 neurons
(Gliogenesis similar, but GBs typically divide only once to give rise to 2 glia)
Doing it over and over againS
(there are 5 waves of NB segregation in *Drosophila* S1-S5)
Cell migration
Cell death
Axon pathfinding
Synapse formation

* These are the only aspects of neurogenesis whose genetic regulation we'll discuss this week.

Some numbers:
25 NBs/hemisegment that give rise to ~200 neurons
(40 motor; 5 neurosecretory; and 150 interneurons)
Ultimately ~500/2000 neuroectodermal cells/embryo become NBs

5) Key experiments:
Evidence for functional equivalence within proneural clusters
(grasshopper NB ablations; Doe and Goodman, 1985)

Evidence for induction:
Homotopic and heterotopic transplantations
(Technau, Stuettem and Campos-Ortega, 1986; 1991)
ventral cells committed early
dorsal cells not
Heterchronic transplantations (Technau, 1988) and the remarkable
plasticity of the system
Inter-germ layer transplants (Technau and Campos-Ortega, 1986;
Beer 1987) - no transdetermination

Confusing terminology:
proneural genes (e.g. AS-C family members) - promote neuroblast formation
neurogenic genes (e.g. Notch, Delta, mastermind, big brain, Enhancer of split, neuralized) - promote epidermoblast differentiation
Why the discrepancy?

6) Genetic control of neurogenesis - more DV and AP inputs
Proneural gene expression in presumptive rows and columns
4 rows, 3 columns per hemisegment (S1 and S2)
Neurogenic genes inhibit proneurals (Dl→N→E(spl)--|AS-C)

7) More key experiments
N and Dl mutant cells transplanted into a wild type host can become epidermal!
Transplanted E(spl) mutant cells always become neural
Implications for signal sending and receiving
Lack of cell autonomy of N (Heitzler and Simpson, 1991) - cells with 3 copies of N+ preferentially become epidermal

8) What are the gene products of the proneurals and neurogenics and how do they work?
AS-C - bHLH
N - transmembrane with extracellular EGF repeats and intracellular opa repeat
Dl - transmembrane with extracellular EGF repeats
Ser - transmembrane with extracellular EGF repeats
E(spl) - 8 bHLH + groucho

neur - E3 ubiquitin ligase
Other essential molecules: Su(H), presenilin, fringe, liquid facets (epsin), and (perhaps) Wnt

Data paper for Tuesday's discussion:
Wang W, Struhl G.
Distinct roles for Mind bomb, Neuralized and Epsin in mediating DSL endocytosis and signaling in *Drosophila*.
Development. 2005 Jun;132(12):2883-94.

Review articles (I do not expect you to read these in their entirety, but to read subsections as needed to understand the data paper):

Le Borgne R, Bardin A, Schweisguth F.
The roles of receptor and ligand endocytosis in regulating Notch signaling.
Development. 2005 Apr;132(8):1751-62. Review.

Lai EC.
Notch signaling: control of cell communication and cell fate.
Development. 2004 Mar;131(5):965-73. Review.

Study questions for Tuesday:
1) Describe in 1-2 paragraphs how Notch signaling works. Start outside the cell with the Delta-Notch interaction, go through the cytoplasm, and end in the nucleus with the relevant transcription factors bound to an enhancer.

2) Now describe the known post-translational modifications to the signals (Delta and Serrate) and explain how they are thought to impact signaling.