The Development of the Peripheral Nervous System in the Fruit Fly *Drosophila*

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**Peripheral senses**

- Sight: eyes
- Smell: olfactory receptors in antenna (nose)
- Taste: taste receptors in labia and legs (tongue)
- Hearing: Johnston organ in antenna (ear)
- Proprioception: external sensory organs covering entire body (skin)

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**Sensory organs of an adult Drosophila**

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**Hearing: Johnston organ and chordotonal organs**

- **cd**: chordotonal organ
d- **sc**: sensillum chorda
- **bb**: basiconic sensillum
- **cf**: chemosensory hair

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**Hearing in *Drosophila* courtship**

- **pulse song**
- **sine song**

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**External sensory organs: a model to unravel the development of the PNS**

Adapted from Lai and Orgogozo, 2004

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### Mechanosensory organs
- Microchaetae
- Macrochaetae
- Stout and slender bristles of the wing margin

### Chemosensory organs
- Recurved bristles of the wing margin
- Chemosensory hairs of the proboscis and tarsus
- Respond to sugars or salts

### Sensory organ development
- Each sensory organ is composed of various cell types that are clonally related
- The mother cell of each organ is called the sensory organ precursor (SOP)
- SOP gives rise to neuron(s) and support cells via asymmetric divisions
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**Early development of PNS organs**

- Controlled by proneural proteins
- Proneural proteins are basic helix loop helix (bHLH) proteins
- Proneural proteins are expressed in small patches of ectodermal cells: proneural clusters
- They are necessary and sufficient to form PNS organs
- They not only specify the neuronal lineage but also the subtype of PNS organ
- There are 5 proneural proteins in flies: Scute, Achaete, Amos, Lethal of Scute, and Atonal

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**bHLH proneural genes in PNS**

- *achaete* and *scute*: external sensory organs, some multidendritic organs
- *atona*: chordotonal organs, photoreceptors, one type of olfactory hair
- *amos*: some multidendritic organs, two types of olfactory hair
- *daughterless*: necessary for almost all types, as a partner with others

Bertrand et al., 2002

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### Proneural proteins and Notch signaling during sensory bristle development

- **Lateral inhibition**
- **Asymmetric division**

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### Notch signaling in the specification of the SOPs

**Presumptive SOP**

**Ectodermal Cell**

- Proneural
- \( E(spl) \)
- \( \Delta \)
- \( \text{Notch} \)

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### Senseless is essential for proper SOP formation

**Presumptive SOP**

**Ectodermal Cell**

- Senseless
- Proneural
- \( E(spl) \)
- \( \Delta \)
- \( \text{Notch} \)

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Loss of external sensory organs in a sens clone

Sens zinc fingers are highly conserved

Loss of Scute expression in sens mutant clones in the wing disc

Nolo et al., 2000 in senseless clones (dark)
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**Ectopic expression of senseless induces PNS and proneural gene expression**

![Image of senseless expression](image1.png)

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**Senseless synergizes with proneural proteins**

Ectopic Senseless OR Ectopic Scute

Ectopic Senseless AND Ectopic Scute

![Image of Senseless expression](image2.png)

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**achaete promoter-luciferase reporter construct and S2 cell transcription assay**

Expression construct

Reporter construct

Control vector

S2 cells

Firefly Luciferase

Renilla Luciferase

![Image of luciferase assay](image3.png)
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**Low levels of Sens repress ac transcription in a DNA-binding-dependent manner**

![Graph showing repressive effect of Sens on ac transcription](image)

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**Senseless summary**

- Zn-finger transcription factor (4 C2H2 domains)
- Nuclear protein expressed in SOP I and SOP II
- Required to specify some SOPs in adult PNS
- Directly dependent on proneural gene expression
- Induces proneural gene expression when ectopically expressed
- Represses PNS development at low concentrations via binding of DNA
- Promotes PNS development at high concentration via synergism and binding with proneural proteins
- Is necessary and sufficient to form pns

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Asymmetric divisions in the adult external sensory lineages (bristles)

- Extrinsic (Notch signaling)
- Intrinsic (fate determinants)

Sensory lineage in WT and Notch mutations

Asymmetric localization of cell fate determinants

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Asymmetric localization of cell fate determinants

Sensory lineage in WT and numb mutations

Wild-type  Loss of numb  Gain of numb
= Gain of Notch = Loss of Notch

Sensory lineage in WT and neuralized mutations

Wild-type  Loss of neur  Gain of neur
= Loss of Notch = Gain of Notch
Differentiation of ESO are dependent on:

- Proneural proteins that specify subtype
- Neural type selectors: cut, pox-neuro
- Pan-neuronal genes (asense, deadpan, scratch, ...)
- Genes with specific functions in some of the SOP progeny (prospero, Dpax-2, Hairfess, Sui(?) Bar, ...)

Loss of Notch signaling results in aberrant bristle development

Lateral inhibition
Asymmetric division
Loss of Notch

Notch signaling regulates multiple processes during animal development in vertebrates

- Cell fate decision: nervous system, blood, vasculature, pancreas
- Asymmetric divisions: neurogenesis, myogenesis
- Maintenance of undifferentiated state: hematopoietic, muscle and neural stem cells
- Differentiation: skin, oligodendrocytes, bone
Notch signaling is aberrantly regulated in a variety of human diseases

- Developmental disorders: bone, blood vessels, liver, heart, face, eye
- Cancer: T-Cell leukemia, breast cancer, lung cancer
- Cerebrovascular dementia: CADASIL
- Demyelinating disorders

An adult mosaic screen to find novel genes involved in the Notch pathway

- Brand & Perrimon (1993)
- Xu & Rubin (1993)

Increased number of pIIb progeny in mutant clones

- Jafar-Nejad et al., 2005
sec15 encodes a component of the exocyst

Lipshutz & Mostov, 2002

WT sec15

Is sec15 required for the signal sending or receiving cell?

Jafar-Nejad et al, 2005

Localization of all intrinsic determinants is normal in sec15 mutant clones

WT sec15

sec15 encodes a component of the exocyst

Is sec15 required for the signal sending or receiving cell?
Sec15 functions upstream of the S3 cleavage of Notch

- Sca>NEXT
- sec15+
- sec15−

Similarities between sanpodo and sec15 phenotypes

- Spdo is a four-pass transmembrane protein
- Its loss of function causes pIIa to pIIb transformation in embryonic PNS
- Functions upstream of the S3 cleavage of Notch but downstream of Numb

O'Connor & Skeath, 2003
Skeath & Doe, 1998
Dye et al., 1998

Spdo and Sec15 function in the same pathway in bristle development

- spdo−
- spdo− sec15−
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**Spdo is upregulated and mislocalized in sec15 pI cells**

- anterior arrow

- z section
- xy section

- WT
- sec15
- WT
- sec15

Jafar-Nejad et al., 2005

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**Spdo is upregulated and mislocalized in sec15 pII cells**

- anterior arrow

- z section
- xy section

- WT
- sec15
- WT
- sec15

Jafar-Nejad et al., 2005

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**Spdo and Delta colocalize in WT and sec15 SOPs**

- anterior arrow

- z section
- xy section

- WT
- sec15
- WT
- sec15

Jafar-Nejad et al., 2005

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- Endocytosed Delta colocalizes with Spdo in WT and sec15$^3$ SOPs
- Note the basal localization of the endocytosed Delta in mutant cells

Rab11 is strongly upregulated in the apical areas of sec15 clones

A model for Sec15 function

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