

During development, neurons undergo axon guidance and soma guidance.

Axon can migrate responding to attractive cues and repulsive cues.

ROBO/SLIT system

- ROBO receptors: belongs to the immunoglobulin superfamily.
 - 1 type in *C. elegans*, 3 in *Drosophila* and vertebrates, 4 in humans.
 - Contains immunoglobulin-like domains and fibronectin type III repeats
- SLIT ligands: contains 4 leucine rich repeat (LRR) domains
 - 1 type in *C. elegans* and *drosophila*, 3 homologs in vertebrates.
 - Contains EGF-like repeats, laminin G-like repeats, and cysteine knot.

EPH/Ephrin system

- EPH receptors: two classes A and B, can have different responses in different neurons
 - Cysteine rich domains
 - Fibronectin type III domains
 - Kinase domain
 - PDZ domains
 - Forward signalling repels growth cone, causes growth cone collapse
- Ephrin ligands: two classes A and B
 - Anchored by GPI
 - Contain intracellular PDZ domain (bidirectional signalling)
 - Reverse signalling promote growth cone survival

Semaphorin - plexin/neuropilin system

- Class 3 semaphorin ligands: seven members SEMA3A~SEMA3G
 - Binding with receptor causes growth cone collapse, repel growth cone
 - Exception SEMA3E, can bind to D-type plexin PLXND1 and repels growth cone.
 - However, SEMA3E can optionally recruit NRP1 and VEGFR2, which promotes growth cone survival
- Neuropilin: two classes, NRP1 and NRP2
 - Act as coreceptors with SEMA3 ligands
 - Act as receptor for VEGF, promotes growth cone survival with coreceptor X.
- Plexin A type receptors: four classes PLXNA1~4
 - Contain intracellular domains to allow signal transduction.
 - **Explant assay shows KO of PLXNA3/4 show lack of repulsion, shows PLXNA4 important for repulsion.**
 - **KO of PLXNA4 show neuron grow into no neuron zone in WT mice.**

VEGF - VEGFR:

- All VEGF isoforms bind to VEGFR2
- VEGF exon 6 7 important to bind with NRP1
- VEGF downstream signalling PI3K - promote growth.

Culturing in vitro and observing growth cone turning can assess promoting/inhibitory effects of signalling molecules.

Dil labelling can stain the neuron axon, visualise the neuron pathway.

- *Drosophila* commissural neuron crossing in nerve cord (ROBO/SLIT system)
 - ROBO receptors is expressed in neurons at both sides.
 - SLIT ligand is expressed by midline glia
 - Low ROBO receptor expression - less repulsion - crossing - upregulate ROBO expression
 - High ROBO receptor expression - do not cross
 - ROBO mutants: always crossing forming “roundabouts”
- Commissural neuron crossing
 - ROBO is expressed by neurons
 - SLIT is expressed by glial cells to restrict crossing to the ventral commissure in the spinal cord
 - In optic chiasm: SLIT expressing glia form a corridor around the chiasm, guide crossing of retinal ganglion cells
 - **In slit mice mutants, crossing is not restricted to the single corridor**
- EPH/Ephrin in murine optic chiasm crossing:
 - EphrinB receptors expressed in ipsilateral RGCs, originating from temporal RGCs
 - EPH expressed at the chiasm, repel the ipsilateral RGCs
- NRP1 signalling in optic chiasm crossing:
 - NRP1 is expressed by contralateral RGCs, **KO of VEGFA or NRP1 lead to less contralateral crossing**
 - During crossing, SEMA3 ligand is not expressed, VEGFA is expressed
 - VEGFA - NRP1 signalling promotes growth cone, attract contralateral crossing.

In summary, during optic chiasm crossing:

- ROBO/SLIT restrict the position of the chiasm
- EPH/Ephrin repels ipsilateral RGCs
- NRP1/VEGFA promotes contralateral RGC crossing