Control of: neuron proliferation, neuron cell death

Overall, the number of neurons decrease over developmental timeline, with the greatest rate of decrease during the juvenile stage.

Apoptosis: programmed cell death, opposed to necrosis induced by injury

- Rapid process, cell fragments are cleared by macrophages
- Morphological characteristics: cytoplasmic blebbing + nuclear fragmentation
- Biochemical characteristics: activation of caspase + DNA fragmentation
  - Influx of ions or the activation of Bcl2, cause oligomerisation
  - Bcl2 channel form, cytochrome-C move out of mitochondria
  - Cytochrome C bind to apaf-1 adaptor, activate procaspase 9
  - Procaspase 9 autocleave, release caspase 9, further cleaves procaspase 3
  - Procaspase 3 cleaved by 9 to become caspase 3, induce further downstream degradation of cell components

Apoptosis is important for development, lack of apoptosis can lead to overproliferation

Procaspase 9 KO lead to brain overgrowth in mice, failure to close neuropore.

Regulation of apoptosis: presence of survival signals / presence of apoptotic signals:

- **Grafting experiment shows less neuron death in dorsal root ganglions(DRG) innervating the limbs.**
  - Neurotrophic hypothesis: target tissues release trophic factors, neurons compete for the factor to survive, neuron with the strongest connection to the target tissue survive. retrograde transport along the axon required.
  - **Discovery of Nerve growth factor (NGF): sarcoma cells would prevent neuron death, culture medium of sarcoma can promote neuron survival and proliferation of DRG in vitro.**
  - **Adding snake venom to culture medium induce neuron survival, venom is secreted by salivary gland which produce a lot of NGF.**
- NGF is transported in a retrograde manner
  - **Two compartment set up expose only axon ending to NGF, however this also induce neuron survival**

Specificity of neurotrophin factors:

- NGF only induce proliferation in DRGs, while BDNF only induce proliferation in nodose ganglions.
- Neurotrophic factors bind to specific Trk receptors
  - NGF bind to TrkA receptors, which is potentiated by p75 coreceptor, binding to p75 in absence of TrkA induce apoptosis.
  - Neurotrophin (NT4/5) and BDNF bind to TrkB receptors
  - NT3 bind to TrkC receptor

Time dependency of neurotrophic factors:

- Some neurotrophic factors only induce effect in early stage neurons, no effect however in late stage neurons

Dependency switching of neurotrophic factors:

- E.g. trigenminal nerve is dependent on BDNF during early developmental stages, but switch to NGF in later stages

Nerve growth factor (NGF) signalling pathway:

NGF —> TrkA RTK —> PI3K (survival) + Ras-MAPK (growth and differentiation) + PLC (synaptic function)

NGF binding with TrkA ativates PI3K pathway which inhibits cell death:

- PI3K activates AKT
- AKT phosphorylates bad, allow sequestration of bad-P by 14-3-3, prevent Bad from activating Bcl2

Sources of neurotrophic factors:

- Target derived
- Glial cell derived
- Endocrine derived
- Autocrine / paracrine derived