Neuron-target interaction

1. **Synapse formation between presynaptic and postsynaptic cells**
   - Synaptogenesis in neuromuscular junction (NMJ)
   - Central synapses form in a similar manner as in NMJ.
   - Synapse elimination - A large number of synapses eliminated.
     Proposed model:
     Active axon triggers the generation of local retrograde signal from target cells.

2. **Neurotransmitter phenotype of neurons**
   - Phenotype changes can occur after migrating to the final destination.
   - Influenced by signals from target cells

3. **Regulation of survival of neurons by signals from target cells.**
   - **Neurotrophic factor hypothesis**
     - Lack or limited supply of neurotrophic factors by surrounding cells leads to cell death.

   **Target cells secrete a variety of neurotrophic factors.**
   - Neurotrophins
   - Cytokines such as CNTF (ciliary neurotrophic factor)
Control of Neuronal Phenotype

* Influence of Neuron-Target Interaction is not limited to synapses.
  Motor-neuron-Muscle cell interaction ⇒ synapse formation and maturation

* Neuron-Target Interaction can cause phenotype change.

FIGURE 6. The growth of dendrites can be controlled by glial cells. The morphology of cultured sympathetic neurons is visualized by injection of the dye Lucifer Yellow and observation with fluorescence optics. When grown in the absence of glia (A), the neurons exhibit long axons and few, if any, dendrites. When cocultured with glial cells from sympathetic ganglia, in contrast, the neurons produce many dendrites as well as an axon (B). The latter has branched (B, arrowheads) in both cases. Dendrites are identified as being much shorter and thicker than axons, and gradually tapering rather than having a constant, narrow bore like axons. The dendritic nature of these processes has also been confirmed using antibody markers and by electron microscopy. (From M. Tropea et al., 1988. Gila 1: 380–392.)
Neuronal phenotype

1. Cell lineage
2. Environmental factors

Phenotype change by target tissue
example: Sympathetic ganglia
most neurons produce NE and NPY
neurons innervating to sweat gland-ACh and VIP
(originally noradrenergic but switched to cholinergic)
Instructive factors
- produced by target cells
- determine phenotype of neurons

Cholinergic differentiation actor (CDF)
= Leukemia inhibitory factor (LIF) see p. 442-443
Ciliary neurotrophic factor (CNTF) see p. 450-451
Neurotrophic factors: support neuronal survival

Targets, presynaptic neurons and glial cells control neuronal survival and growth.

Neurotrophins
NGF, BDNF, NT-3, NT-4/5, NT-6
Retrograde axonal transport

Cytokines
CNTF, LIF

Growth factors
FGFs, IGFs, GDNF, PDGF, TGFs
Nerve growth factor (NGF)

1. The first neurotrophic factor discovered
2. Supports neuronal survival of populations of neurons
3. Induces neuronal differentiation of populations of neurons

Sympathetic ganglion Fig. 8, p. 445 and Box B

Trk receptor (high affinity)
Neurotrophins: NGF family (NGF, BDNF, NT3, NT4/5, NT6)
Act on Trk receptors and p75(low affinity) receptor
Retrograde transport
Differential effects
Neuronal cell death during development

- Before a stable mature nervous system is formed, many neurons die.
- In vertebrate, ~3/4 of neurons die during early embryonic development.
- Cell death is an integral part of normal embryonic development.

Programmed cell death and neurotrophic hypothesis

Anti-NGF Ab causes almost total degeneration of sympathetic ganglia.

Survival of a group of neurons may depend on exposure to a specific factor (NGF and other neurotrophins, FGFs, CNTF etc) at a critical time of development.

\[ \text{NGF} \Rightarrow \text{TrkA} \uparrow \Rightarrow \text{Bcl-2} \uparrow \Rightarrow \text{Apaf-1} \downarrow \Rightarrow \text{no caspase activation} \Rightarrow \text{cell survival} \]
\[ \downarrow \text{ (death inhibitor)} \]
\[ \downarrow \]
\[ \text{PI3K} \Rightarrow \text{Akt (PKB)} \Rightarrow \text{Bad (death promoter)} \downarrow \]

No NGF \Rightarrow \Rightarrow \text{Apaf-1. (ATP)} \Rightarrow \text{caspase activation} \Rightarrow \text{cell death} \]