Axonal growth and its regulation by the environment

The regeneration of severed axons

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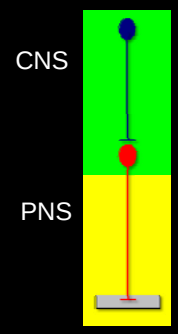
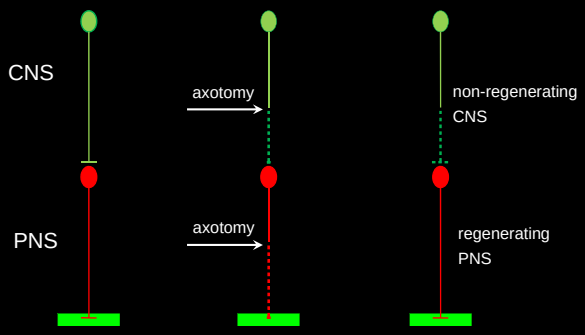
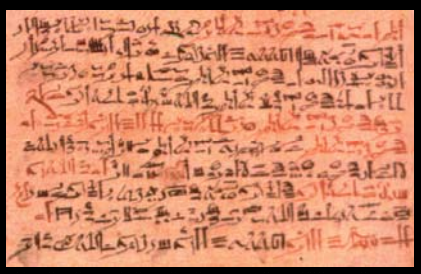
The motor pathway



PNS is regenerating - CNS is not



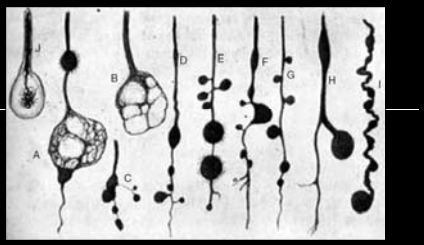
Injury of the spinal cord – an ailment not to be treated (an Egyptian papyrus dated 1550 BC)



One having a dislocation in a vertebra of his neck …
he is unconscious of his two legs and his two arms …
his urine dribbles. An ailment not to be treated.

Egyptian papyrus, The NY academy for Medical Sciences

Retraction bulbs (Cajal, 1928)



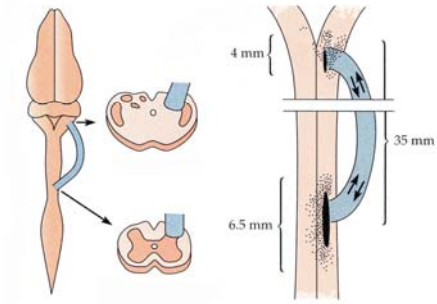
Cajal, "*Degeneration and Regeneration of the Nervous System*", 1928

S. Ramon Y Cajal

Adult CNS axons fail to regenerate – why?

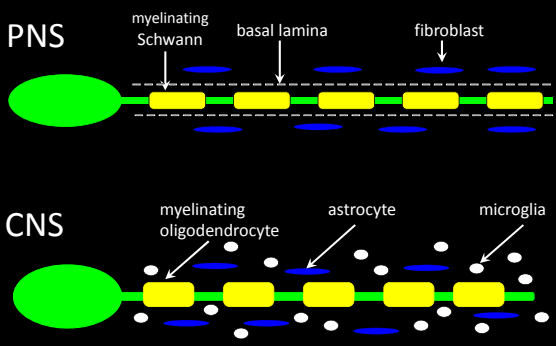
- Adult CNS neurons cannot regenerate their severed axons
- Adult CNS neurons are able to regenerate their severed axons but are prevented from doing so by the CNS environment

CNS neurons regenerate axons through Wallerian degenerated PNS but not CNS tissue

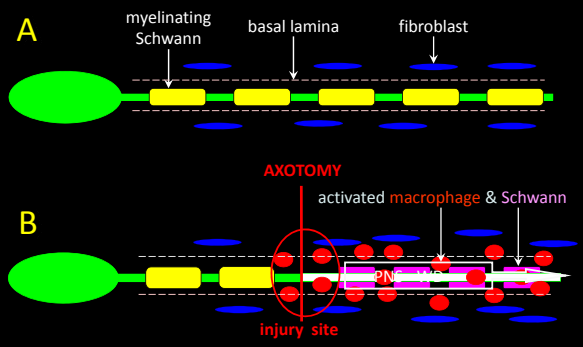


David and Aguayo, 1981; taken from *Neuron to Brain*, Nicholls et al. 2001

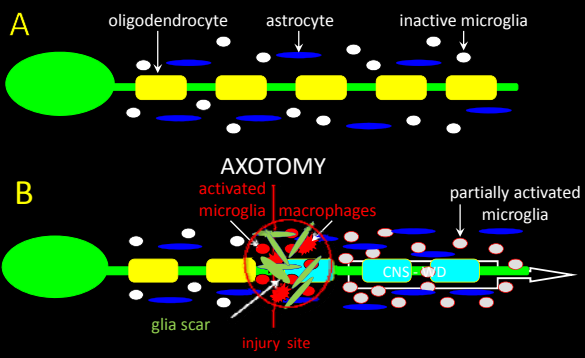
Intact axons in PNS and CNS

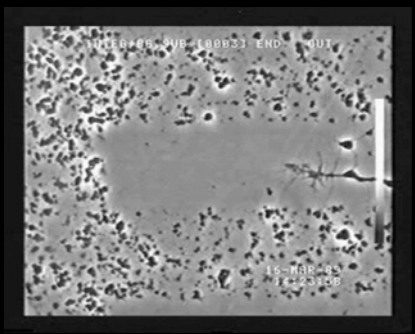


PNS: (A) intact and (B) Wallerian degeneration



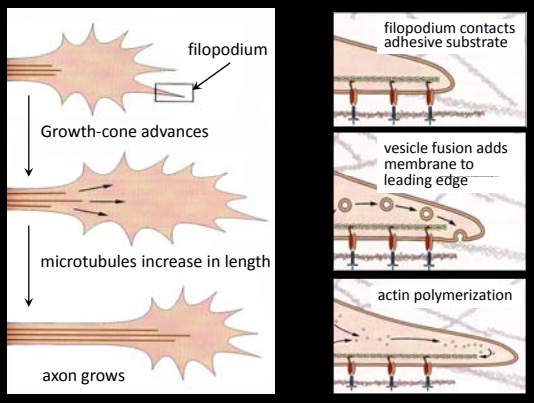
CNS: (A) intact and (B) Wallerian degeneration





- Growth-cones lead axonal growth – regeneration
- Growth-cones "test" the environment by extending and retracting filopodia and lamelliodia and then decide if and where to grow
- Several growth-cones for a single axon, each can grow in a different direction – "local" decisions by the growth-cone
- The environment can send "grow", "stop", "retract" and "collapse" signals

The growth-cone

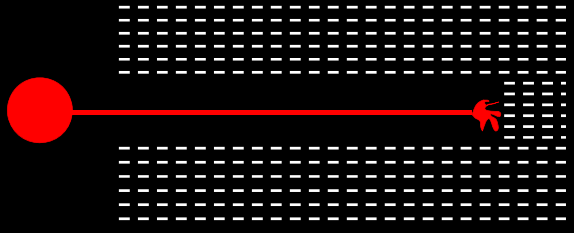


Cytoskeleton (actin filaments and microtubules) are involved in axonal growth

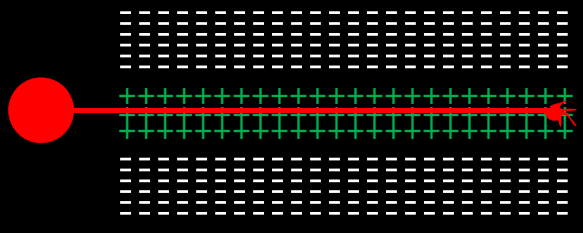
phase contrast | actin filaments | microtubules

from *Neuron to Brain*, Nicholls et al. 2001

Repulsion (-) signals from the environment eliminate axons



Attraction (+) and/or repulsion (-) signals from the environment direct axonal growth



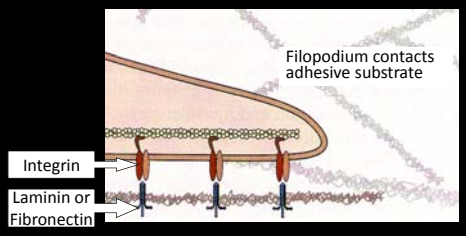
Guidance / Navigation

- **Attraction**
  - fixed & diffusible molecules
- **Repulsion**
  - fixed & diffusible molecules

Attraction by fixed extracellular matrix adhesion molecules

- Collagen, laminin and fibronectin:
  - extracellular matrix molecules produced by non-neuronal cells
- Integrins (α/β):
  - receptors in growth cone

Adhesion molecules in the extracellular matrix and receptors in growth-cone



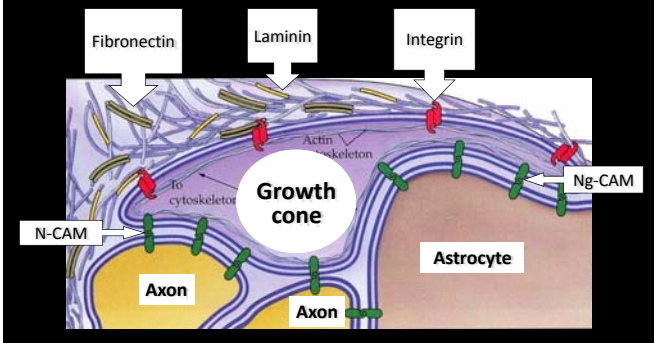
Attraction by fixed cell surface molecules

cell surface receptors – by homophilic interactions

N-CAM – nerve cell adhesion molecule

Ng-CAM – nerve glia cell adhesion molecule, also known as Nr-CAM

Adhesion molecules: cell–matrix & cell-cell interactions



Attraction by diffusible molecules

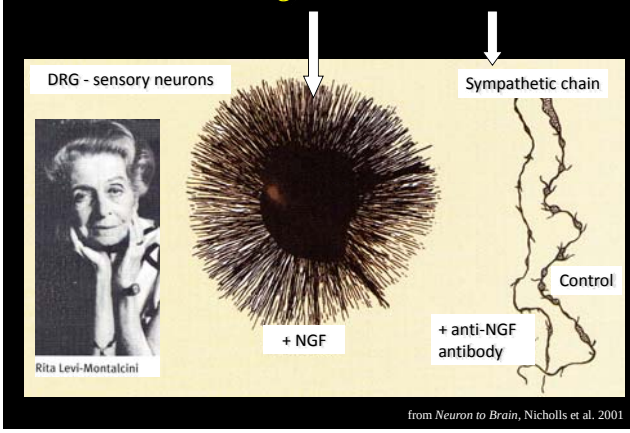
NGF – Nerve Growth Factor (a member of the neurotrophin family of neurotrophic factors)

NGF – produced by target cells that are innervated by NGF responsive nerve cells and by non-neuronal cells

NGF receptors – TrkA and $p75^{NTR}$ in growth-cone

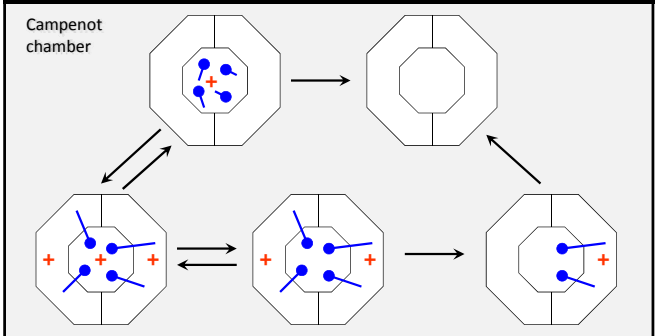
- TrkA – high affinity and NGF specific
- $p75^{NTR}$ – low affinity and shared with other neurotrophins

NGF: axonal growth & cell survival



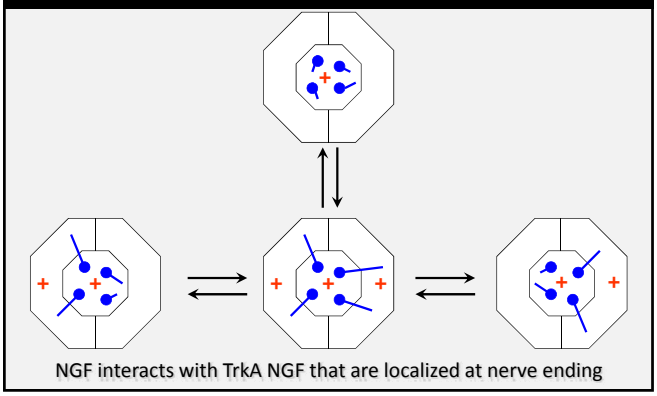
from *Neuron to Brain*, Nicholls et al. 2001

NGF dependent survival of sympathetic neurons



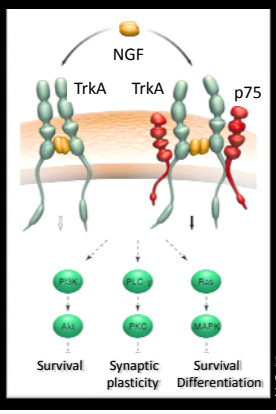
NGF interacts with TrkA receptors that are localized at nerve ending

NGF dependent growth & maintenance of sympathetic neurons axons



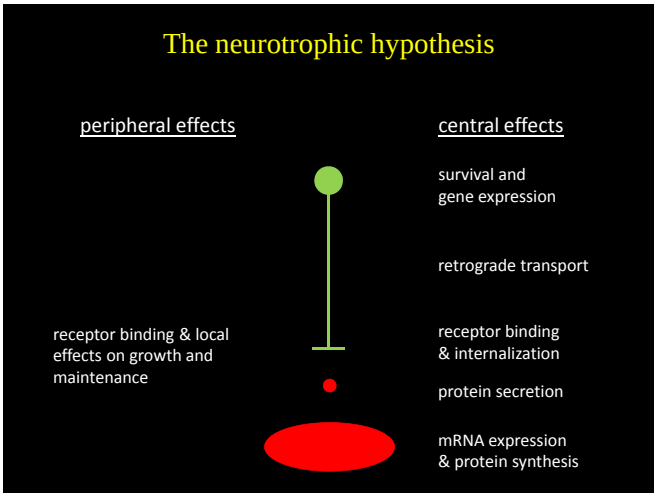
NGF interacts with TrkA NGF that are localized at nerve ending

TrkA and TrkA/p75^{NTR} signal survival

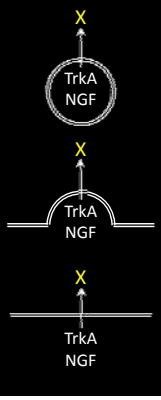


Nykjaer, Willnow & Petersen, *Current Opinion in Neurobiology* 2005

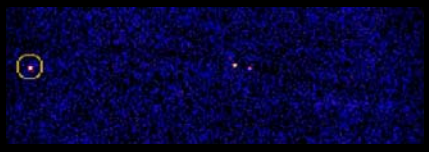
The neurotrophic hypothesis

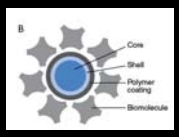


NGF/TrkA complex is internalized to the cell body and retrogradely transported



Retrograde transport of QD-NGF
Live imaging quantum-dot (10-20 nm) analysis





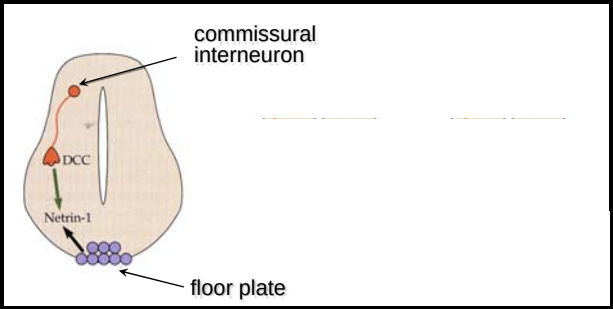
Cui et al., PNAS, 2007

Attraction by diffusible molecules

Attraction by diffusible molecules

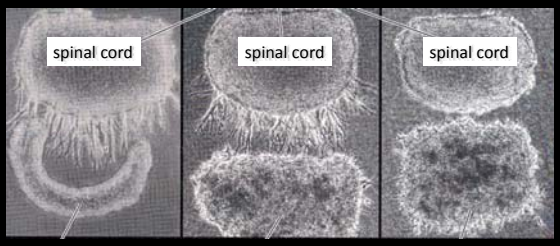
- NGF (TrkA receptor in growth-cone)
- Netrin-1 (DCC receptor in growth-cone)

Navigation in the spinal cord



from *Neuron to Brain*, Nicholls et al. 2001

Attraction by diffusible molecules



floor plate Netrin-1 control

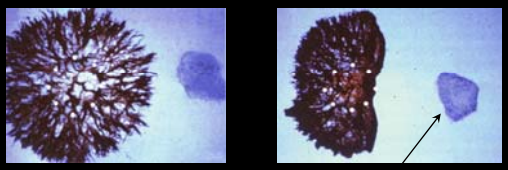
from *Neuron to Brain*, Nicholls et al. 2001

Repulsion by diffusible molecules

Semaphorins – produced by non-neuronal cells

Neuropilin – receptor in growth-cone

Repulsion by diffusible molecules



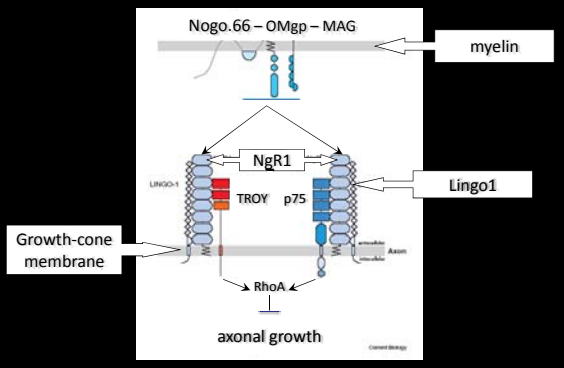
control semaphorin III

from *Neuron to Brain*, Nicholls et al. 2001

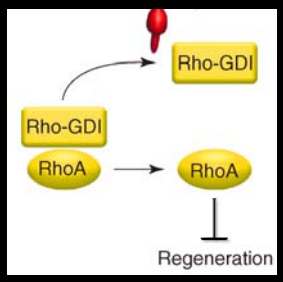
Repulsion by fixed molecules

- Myelin of oligodendrocytes & Schwann cells
  - MAG [myelin associated glycoprotein] (PNS & CNS)
  - Nogo (CNS)
  - OMgp [oligodendrocyte-myelin glycoprotein] (CNS & PNS)
- Astrocytes
  - Chondroitin sulfate proteoglycans

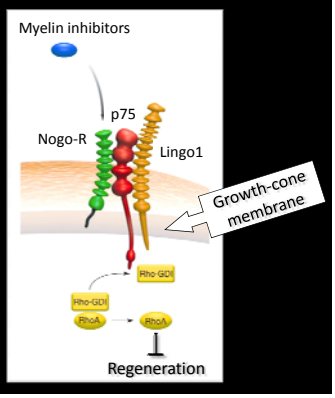
NgR1/Lingo1/(p75^{NTR} or TROY) receptor complex binds Nogo.66, OMgp and MAG



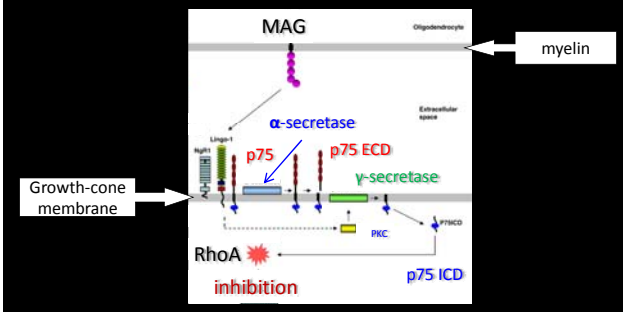
Nogo-R/Lingo1/p75^{NTR} signal growth-arrest



Nykjaer, Willnow & Petersen,
Current Opinion in Neurobiology 2005



Signaling inhibition by MAG activated NGR1/Lingo1/p75 complex

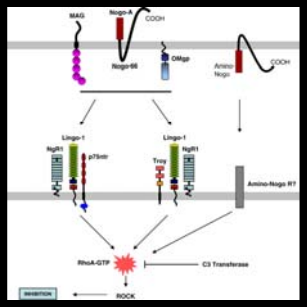


after Nagarathnamma and Filbin,
J. Cerebral blood flow & metabolism, 2007

Nogo receptor – NgR – and its ligands
(NgR1, NgR2 and NgR3)

- Nogo, MAG and OMgp inhibit regeneration in-vitro
- NgR1 binds Nogo-66, MAG and OMgp; NgR2 binds MAG
- NgR1 forms a receptor complex with Lingo-1 and either p75^{NTR} or TROY; the latter two are members of TNF receptor family
- p75^{NTR} and TROY generate signaling transduction that inhibits regeneration by activating RhoA/ROCK
- Inhibition of RhoA overrides inhibition of regeneration

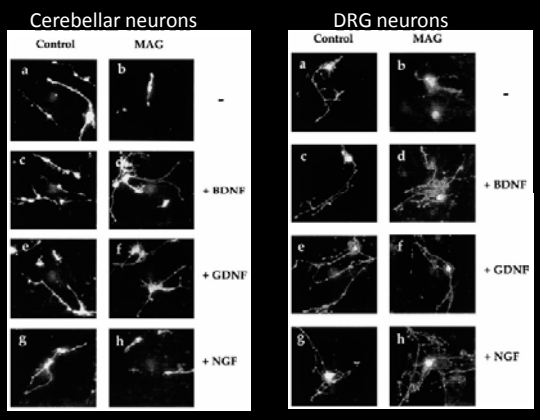
NgR is the receptor for MAG, OMgp and Nogo-66 but not for amino-Nogo



after Nagarathnamma and Filbin, J. Cerebral blood flow & metabolism, 2007

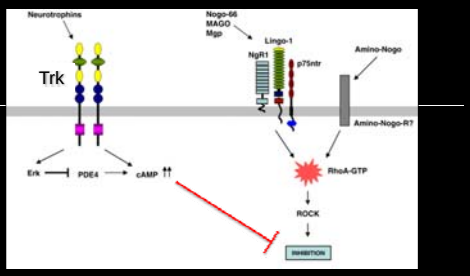
PirB inhibits regeneration after binding Nogo, MAG and OMgp

Neurotrophins override inhibition by MAG



Cai et al 1999

Neurotrophins counteract growth inhibition by elevating cAMP levels



after Nagarathnamma and Filbin,
J. Cerebral blood flow & metabolism, 2007

cAMP regulates myelin-induced inhibition

- High cAMP levels in embryonic DRG cells that normally regenerate in the presence of myelin
- Low cAMP levels in adult DRG cells that normally do not regenerate in the presence of myelin
- Elevation of cAMP levels overrides growth inhibition in adult axons
- Neurotrophins override inhibition by elevating cAMP levels

Axonal growth is regulated by the environment (neurons, non-neuronal cells & extracellular matrix)

- Molecules from the environment direct axonal growth by attraction and/or repulsion
- Molecules from the environment maintain axons in place
- Molecules from the environment induce growth-cone collapse and axon elimination