Events following axontomy (cutting of the axon):

- Fragmentation of distal axons stump, debris cleared away by macrophages.

Different nerve regeneration response to axon injury:

- In PNS: macrophage clears away the debris
- In CNS: no macrophage clearance of debis. Inhibitory substance prevent axon regeneration, astrocytes become reactive astrocyte, also inhibit regeneration
- In DRG: If PNS axon is injured and regenerated, an injury in the CNS can be regenerated as well. This is due to the presence of intracellular cAMP. **Experiment shows adding cAMP to leision site induce regeneration**.

Regeneration events:

- Wallerian degeneration:
    - Recruitment of macrophages to the injury site.
    - Redifferentiation and proliferation of schwann cells.
    - Degradation of surrounding myelin, removal of debris.
- Axon regeneration:
    - Integrin bind with laminin, promote axon growth via tensin transduction
    - Neurotrophin-3 (NT-3) bind with TrkC to promote axon survival
    - BDNF bind to p75 NTR to promote axon growth

Genetic screen identification of genes involved in neuron regeneration

- Ced-1: gene involved in engulfment and regeneration signalling
    - **In Ced-1 mutants, debris remain around the injury site, restore Ced-1 in neurons did not rescue(not an intrinsic factor)**
    - **Immunofluorescence shows Ced-1 co-localise with both early and late endosomes (Phagocytosis)**
    - **Restore extracellular domain in muscle cells allow rescue (act as signalling & adhesion molecule)**

Reprogramming of the schwann cell, autophagocytosis of myelin:

- Myelin act as an inhibitory substance, through the p75 receptor, activate Rho GTPase which inhibits microtubule assembly.
- After axon injury, schwann cells redifferentiate into repair mode, promote autophagocytosis of myelin within the cytoplasm.

- Axon membrane have integrin (receptor), bind to laminin in the extracellular matrix, signal through the PI3K pathway and GSK3 to promote microtubule polymerisation and promote growth cone.

- Tensin is an intracellular protein which contains a SH2 domain, can bind to integrin receptor phosphorylated domain and activate nerve regeneration.
    - **Expression of tensin-1 in injured neurons in tensin-1 mutant C. Elegans shows rescue effect.**
    - **Mutations in different domains of tensin shows the SH2 domain and the PTB domain is important for regneration. SH2 domain of tensin interact with MAPK RTK receptors**
    - **Pull-down assay shows the PTB domain of tensin binds to the PAT-3 intracellular domain of integrin**

- Intrinsic mechanisms in the regenerating neuron: Neurons have differential regenerative abilities in the same culture.
    - Series of biogenesis events underlying the restructuring of the axon (membrane remodelling, cytoskeleton formation, axon transport)
    - Biogenesis within the cell is regulated by master regulator gene mTOR, which is activated by the PI3K pathway and inhibited by PTEN
    - Neurotrophin-3 / TrkC signalling activates PI3K pathway
    - Interleukin-6 & Leukemia inhibitory factor activates the JAK/STAT3 pathway, promote cytoskeleton remodelling
    - cAMP activates PKA, which inhibits Rho, promote microtubule assembly
        - cAMP also activates CREB transcription, which promotes microtubule assembly.