WALLERIAN DEMYELINATION
Chronicle of a cellular cataclysm
PERIPHERAL NERVE DEMYELINATION

- Peripheral demyelination results from the loss of the myelin sheath in peripheral nerves

- Demyelination is the main cause of peripheral nerve diseases

- Demyelination is sufficient to impair peripheral nerve functions

- Chronic demyelination leads to axonal degeneration and loss
PERIPHERAL NERVE DEMYELINATION

- Traumatic demyelination: Wallerian demyelination

- Acquired diseases demyelination: Diabetic peripheral neuropathy, CIDP, GBS, leprous neuropathy, iatrogenic peripheral neuropathies

- Hereditary peripheral neuropathies: Charcot-Marie-Tooth disease type 1 (70% of all CMTs)
PERIPHERAL NERVE DEMYELINATION:

PHYSICIANS vs SCIENTISTS VIEW

For physicians demyelination is the status of a nerve that has lost its myelin.

For scientists demyelination is the cellular process that leads to the loss of myelin.
PERIPHERAL NERVE DEMYELINATION:
DEMYELINATION PROCESS

- While the causes that lead to Schwann cell demyelination (metabolic, infectious, traumatic, iatrogenic, immune...) are very diverse, the outcome is very similar.

- Outcome of demyelination: myelin fragmentation in myelin ovoids, nerve inflammation, macrophages recruitment, effective remyelination or attempts.

- What about the cellular processes?
When Schwann cells demyelinate, they do not die. They de-differentiate to a demyelinated cell. They then can remyelinate intact or regenerated axons.
PERIPHERAL NERVE DEMYELINATION:
WALLERIAN DEMYELINATION AS A MODEL FOR
DEMYELINATION PROCESS

- Easy to induce in animals (nerve crush or cut)
- Synchronized demyelination (vs chronic demyelination)
- Massive demyelination and significant behavioral impairment
WALLERIAN DEGENERATION =
AXONAL DEGENERATION AND WALLERIAN DEMYELINATION

- Axonal degeneration
- Remyelination
- Demyelination

- Injury
- Regenerated nerves
- Macrophages
- Reactive Schwann cells
- Axonal degeneration

0 to 5 days

5 to 30 days

> 1 month
SUCCESSIVE STEPS THAT LEAD TO DEMYELINATION

injury

TRIGGER → AMPLIFICATION → REPROGRAMMING → MYELIN DESTRUCTION

0h  1h  4h  24h  3 days
STEP 1: THE TRIGGER

TRIGGER → AMPLIFICATION → REPROGRAMMING → MYELIN DESTRUCTION

0 → 1h → 4h → 24h → 3d
STEP 1: THE TRIGGER
STEP 2: THE SIGNAL AMPLIFICATION

injury

0 1h 4h 24h 3 days

TRIGGER  AMPLIFICATION  REPROGRAMMING  MYELIN DESTRUCTION
STEP 2: THE SIGNAL AMPLIFICATION
STEP 3: THE REPROGRAMMING

injury

TRIGGER

AMPLIFICATION

REPROGRAMMING

MYELIN DESTRUCTION

0 1h 4h 24h 3 days
STEP 3: THE REPROGRAMMING
STEP 4: THE MYELIN DESTRUCTION

injury

TRIGGER  AMPLIFICATION  REPROGRAMMING  MYELIN DESTRUCTION

0  1h  4h  24h  3 days
MYELIN OVOIDS, THE LAST DEGENERATIVE STEP

Ramon y Cajal 1959

Histology 1970’s

CARS live imaging 2017

7 days post crush injury in mice
STEP 4: THE MYELIN DESTRUCTION

Ghabriel and allt, 1979
PERIPHERAL NERVE DEMYELINATION: CELLULAR PROCESSES

- When Schwann cells demyelinate they do not die
- They de-differentiate to a demyelinated cell
- This process is stereotypic and sequential
- The process is common to all demyelinating diseases
- They then can remyelinate intact or regenerated axons
HOW TO PREVENT DEMYELINATION?

FOCUS ON MITOCHONDRIA
IN VIVO TIME LAPSE IMAGING OF MITOCHONDRIA
MITOCHONDRIAL CALCIUM RELEASE AFTER CRUSH
TRO19622 BLOCK CALCIUM RELEASE IN VIVO
BLOCKING CALCIUM RELEASE IMPROVES MYELINATION AND NERVE CONDUCTION IN DIABETIC MICE...
BLOCKING CALCIUM RELEASE IMPROVES MYELINATION AND NERVE CONDUCTION IN CMT1A RATS...

VDAC inhibition prevents demyelination

VDAC inhibition improves g-ratio and prevents axon loss

VDAC inhibition increases NCV and amplitude
BLOCKING CALCIUM RELEASE IMPROVES CLINICAL SCORE AND NERVE CONDUCTION IN GBS RATS (EAN)

In collaboration with J. Devaux
PERIPHERAL NERVE DEMYELINATION

Blocking mitochondrial calcium release may represent a new efficient and safe treatment for different forms of demyelinating peripheral neuropathies
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