Wallerian degeneration
the innate immune response of the PNS to traumatic injury

Macrophage and Schwann cell activation &
the cytokine network of Wallerian degeneration

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PNS is regenerating - CNS is not

CNS

axotomy

non-
regenerating
CNS

regenerating
PNS

PNS

axotomy

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

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

A

myelinating Schwann
basal lamina
fibroblast

AXOTOMY

activated macrophage & Schwann

injury site

B

Wallerian degeneration
Augustus Waller (1850)

Intact PNS: myelinated axon

Normal PNS Wallerian degeneration

- Axons degenerate
- Schwann cells reject their myelin
- Schwann cells & fibroblasts proliferate
- Macrophages are recruited from circulation
- Macrophages & Schwann cells are activated to clear and degrade degenerated-myelin

Galectin-3/MAC-2 marks macrophage and Schwann cell activation in normal Wallerian degeneration

- Schwann cell & macrophage activation
- Myelin phagocytosis & degradation

Schwann cell & macrophage activation myelin phagocytosis & degradation are orchestrated in time

- Slow Wallerian degeneration (slow-WD) in mutant Wld^s (Ola) mice
slow Wallerian degeneration in Wld<sup>e</sup> mice

in-vitro degeneration in Wld<sup>e</sup> mice

in-vivo slow Wallerian degeneration

in-vivo injury domain

in-vitro degeneration

Reichert, Sauda & Rotshenker, J. Neurosci. 1994

PNS: (A) normal-WD and (B) slow-WD

A

activated macrophage & Schwann

proximal domain

distal domain

B

n

injury site

Events associated with Wallerian degeneration

<table>
<thead>
<tr>
<th>normal - WD</th>
<th>slow - WD</th>
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<tbody>
<tr>
<td>Normal regeneration</td>
<td>Delayed regeneration</td>
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<td>NGF is upregulated</td>
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<td>Neuropathic pain – rapid development</td>
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Is there a single mechanism that underlies normal- and slow-Wallerian degeneration and the events associated with them?

Wallerian degeneration is the innate immune response of the PNS to traumatic axonal injury

- Normal-WD results from and is a manifestation of a normal innate immune response
- slow-WD results from and is a manifestation of a deficient innate immune response

Cytokines are the mediators of inflammation

Inflammatory – initiation and progression
- TNFα – tumor necrosis factor α
- IL-1α – interleukin-1α
- IL-1β – interleukin-1β
- IL-6 – interleukin 6
- GM-CSF – granulocyte macrophage colony stimulating factor

Anti-inflammatory – down regulation
- IL-10 – interleukin-10
Cytokines in Wallerian degeneration

1. Mediators of inflammation
2. Activate Schwann cells and macrophages to clear degenerated-myelin
3. Regulate NGF production
4. Nerve growth factors
5. Regulate neuropathic pain

Cytokine Network of Wallerian degeneration

AXOTOMY

TNFα

IL-1α

IL-1β

GM-CSF

IL-6

IL-10

Studying cytokine production

Immune and non-immune cells synthesize and secrete cytokines that bind and activate cognate receptors on immune cells

• transcription – cytokine mRNA expression
• translation – cytokine protein in cells
• secretion – cytokine protein in extracellular space
• which cell type

TNFα, IL-1α & IL-1β mRNA in normal Wallerian degeneration

IL-1α, IL-1β & TNFα proteins in normal Wallerian degeneration

Shamash, Reichert & Rotshenker, J. Neurosci. 2002
TNFα, IL-1α & IL-1β protein in nerve derived non-neuronal cells

IL-1α, IL-1β & TNFα mRNA in Schwann cells & macrophages

IL-1α, IL-1β & TNFα protein in slow Wallerian degeneration

IL-1α, IL-1β & TNFα mRNA in slow Wallerian degeneration

IL-1α, IL-1β & TNFα protein in slow Wallerian degeneration

GM-CSF production in normal and slow Wallerian degeneration
IL-6 production in normal and slow Wallerian degeneration

IL-10 production in normal and slow Wallerian degeneration

Cytokine Network of Wallerian degeneration


normal Wallerian degeneration

slow Wallerian degeneration

Cytokine production in normal Wallerian degeneration

Reichert, J. Neuroinflammation. 2011
**Macrophage recruitment in normal Wallerian degeneration**

**Cytokine production in normal Wallerian degeneration**

**M1-type and M2-type macrophages**

**Are macrophages friend or foe?**

**Cytokine network of Wallerian degeneration**

**Events associated with Wallerian degeneration**

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**Normal - WD**
- Normal regeneration
- NGF is upregulated
- Neuropathic pain – rapid development

**Slow - WD**
- Delayed regeneration
- NGF is not upregulated
- Neuropathic pain – delayed development
Normal regeneration

Normal removal of myelin
macrophage recruitment and activation
Schwann cell activation
myelin phagocytosis

Neurotrophic factors
NGF

Fixed attraction molecules
Schwann cells, basal lamina, collagen

Cytokines regulate myelin removal

• TNFα, IL-1α and IL-1β function as chemoattractant to recruit macrophages
• TNFα, IL-1α and IL-1β up-regulate production of macrophage chemoattractants MCP-1 and MP-1
• GM-CSF activates macrophages and Schwann cells to clear degenerated-myelin by up-regulating Galectin-3/MAC-2
• GM-CSF up-regulates CR3/MAC-1
• cytokines up-regulate myelin phagocytosis

Cytokines regulate neuropathic pain

• TNFα, IL-1α and IL-1β produce spontaneous firing in sensory neurons
• TNFα, IL-1α and IL-1β up-regulate NGF production in fibroblasts and in vascular endothelial cells. In turn, NGF produces neuropathic pain by sensitizing sensory nerve endings/receptors
• IL-6 deficient mice display reduced neuropathic pain
Wallerian degeneration is the innate immune response of the PNS to traumatic axonal injury.

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Normal Wallerian degeneration

- TNFα
- IL-1α
- IL-1β
- GM-CSF
- IL-6
- IL-10

Diagram:
- Pathway indicating normal Wallerian degeneration with cytokines and growth factors involved.

Legend:
- Red arrows indicate inflammatory signals,
- Green arrows indicate regenerative signals.
- Yellow circles represent immune response signals.