The role of the immune system in the generation of neuropathic pain

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Agenda:

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I Definition and clinical presentation
“Pain that **arises from** direct stimulation of **nervous tissue itself**, central or (far more often) peripheral, exclusive of pain as a consequence of stimulation of C fibers by lesions of other bodily structures”

**Key clinical features:**

- hyperesthesia, hyperalgesia, allodynia, and hyperpathia.
- Often coexisting sensory deficit and local autonomic dysfunction.
- The pain generally responds poorly to treatment, including the administration of opioid medications.
Neurogenic, or Neuropathic Pain includes a variety of different entities:

- Any trauma or lesion involving single and multiple nerves
- Trigeminal neuralgia
- Herpes zoster and other mostly viral infections
- Diabetic neuropathia
- Neuromas and Neurofibromas,
- A number of polyneuropathies of diverse type; root irritation, e.g., from a prolapsed disc; spinal arachnoiditis and spinal cord injuries;
- Guillain-Barré syndrome
- Complex regional pain syndrome (CRPS)
- Toxic injury (e.g. Chemotherapeutic agents, such as Vinca Alcaloids, Taxols, Oxaliplatin, Antiretroviral drugs)

- Multiple Sclerosis
- Thalamic pain syndrome of DejerineRoussy;
- Rarely, parietal lobe infarction
- As a rule, lesions of the cerebral cortex and white matter are associated not with pain but with hypalgesia.

Please note that this overview is far from extensive!
Common clinical scenarios with a common thread

- Trauma (e.g. spinal cord injuries)
- Infection (e.g. Herpes zoster)
- Toxins (e.g. palitaxel)
- Metabolic agents (Diabetic polyneuropathia)

All of these etiologies are associated with a robust immune response.

Injured neurons and their associated glial cells release factors that activate resident immune cells and recruit more immune cells from the circulation.
II Animal models of neuropathic pain
Animal models of neuropathic pain

**A Traumatic injury:** SNL: Spinal nerve ligation, CCI: Chronic constriction injury, PSNI: Partial sciatic nerve injury, SNI: Spared nerve injury

**B Myelene sensitisation,**
neurotoxic drugs, streptozocin -> toxic to β-Islets

Does it hurt?

Von Frey or Randall Selitto test

-> In a nutshell:

“Pain like behavior” is measured.

Evaluation of withdrawal reflex:

If a stimulus is applied that physiologically does not evoke a response, but the animal withdraws, the animal is considered to have allodynia.
III Inflammation processes in peripheral nerve injury
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Events in the skin after nerve injury

- Terminals of damaged nerve fibre degenerate
- Mast Cell degranulation
- Activation and numerical increase of Langehans cells - initial secretion of proinflammatory cytokines, release of NO - initial sensitization of nociceptive terminals
- Keratinocytes themselves can release inflammatory mediators, ATP, GFs
- In CRPS and post-herpetic neuralgia Nav-channels and CGRP is upregulated (possibly neuropeptide regulated);
  Higher concentration of TNF-a, IL 1b, 6, 8, chemokines are found

→ Note that the changed micromillieu also acts on the uninjured, none degenerating nerve fibres!
1. Uninjured nerve

2. Initial reaction to injury (~24 hours)

3. Macrophage recruitment; Wallerian degeneration (one week)

4. Schwann cell alignment; axon regeneration (weeks to months)

5. Successful target reinnervation (weeks to years)

**LEGEND**
- **Blue**: peripheral neuron
- **Red**: resident macrophage
- **Yellow**: injury site
- **Activated macrophage**: activated macrophage
- **Green**: myelinating Schwann cell
- **Nonmyelinating Schwann cell**: nonmyelinating Schwann cell
- **Purple**: myelin debris
- **Orange**: apoptotic Schwann cell
- **Gray**: basal lamina
- **Red dot**: cytokines / growth factors
The uninjured nerve

- The endoneurium of an uninjured nerve consists of axons, associated Schwann cells (myelinating and nonmyelinating), and resident, inactivated macrophages.

Wallerian degeneration a brief overview

2. Initial reaction to injury
(~24 hours)

**PNI** -> Degeneration of axon, distal to lesion (24h to several days in primates) -> the severed nerve still shows excitability!

-> The Calcium influx -> Calpain and Ubiquitin-proteasom activation is essential for the next phase:

Axons bead and swell -> catastrophic granular disintegration of the cytoskeleton occurs (within 24h)

- Within 4-7 days the blood nerve barrier (bnb) permeability double, coinciding with peak inflammation, the bnb tightens and second, sustained increase in permeability starting ~4 weeks after transection becomes permeable again (homeostasis?)
Schwann cells – First responders in PNI

• Soon after PNI, denervated myelinating Schwann cells release their myelin (ubiquitin proteasome dependent)

• Schwann cells then proliferate within their basal lamina tubes, produce cytokines/trophic factors (upregulate regeneration-associated genes GAP-43, neurotrophic factors and their receptors, neuregulin and its receptors) phagocytosis of detached debris by macrophages and schwann cells themselves!

-> The proliferation takes place in Bügner bands

• Reaction within the neuron cell body begins: cell soma hypertrophy, displacement of the nucleus to an eccentric position, and dissolution of Nissl bodies.
Immunohistochemistry to visualize axons (PGP9.5) and macrophages (F4/80) in sciatic nerves of rats, after PNI, at the site of injury.

• Activated Schwann cells initiate cytokine/chemokine cascades that amplify and fine-tune the inflammatory response after PNI.

• Macrophages take over debris, and produce factors that facilitate Schwann cell migration and axon regeneration.

• After a lag period, injured axons form a growth cone and begin to regenerate along bands of Büngner formed by Schwann cells.

• Schwann cells that have been chronically denervated (e.g., for a few months) are less supportive of regrowth and are more likely to undergo apoptosis.
Schwann cells as sentinels in orchestrating inflammation and tissue repair - a double edged sword

- Schwann cells sense DAMPs via TLRs -> trigger the build up of an inflammatory millieu necessary for regeneration

-> This micromillieu also influences intact nerve fibres!
Evidence for the involvement of peripheral inflammation in neuropathic pain

- Depletion of macrophages reduces hypersensitivity after PNI
- Higher percentage of M1 macrophages in CRPRs
- Athymic rats (T-cells depleted) show reduced hypersensitivity
- Many proinflammatory cytokines (such as TNF-a) directly stimulate nerve terminals, their respective receptors are upregulated after injury
- Injecting such mediators leads to hypersensitivity
- Note that aggressive suppression of the initial inflammatory response impairs regeneration!

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Enhanced dorsal root ganglion (DRG)-excitability

- Proliferation of satellite cells, recruitment of PBMCs, general upregulation of cytokines and their receptors in all participants
- Enhancement of excitability, recruitment of TRPV1, A1, M8 and Nav channels to the DRG-membrane
- Note that nerve cells can express TLR and release pro-inflammatory mediators themselves!
IV Neuroimmunology in the CNS
Central nervous neuroimmune interactions
• DAMPs, neuregulin-1, MMP-9, CCL2, other pro-inflammatory mediators -> Microgliosis -> Immune response as distant as thalamus!

• Enhances glutamatergic wind up, e.g. GABA-Current polarity reverse, by BDNF!

• Some Anti-neuropathic drugs, with proven efficacy (e.g. Pregabalin) dampen microgliosis
V Translational considerations
Translation in to treatment

• Preclinical models show remarkable effects in alleviating neuropathic pain with the help of immunomodulatory drugs.

• However…

• Clinical evidence is sparse and inconclusive

• **General problems:**

→ Defining adequate subpopulations that will benefit from antinflammatory/immunomodulatory treatment

→ Pain, regardless of origin is multifactorial

→ Treatment in clinical scenarios is often delayed, immunomodulation in animal models is most effective when administered after injury

→ Cytokine and chemokine signalling is redundant! Just blocking TNF-a (e.g. Etarnecept, Infliximab…) might not overrule general inflammation
“Results from those studies have been mixed, and limited by small sample size and patient heterogeneity. Other approaches may include using a single agent to target multiple aspects of the immune pathway to treat neuropathic pain.”
VI Q&A and References
References


