Multiple sclerosis: inflammation and neurodegeneration

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Multiple sclerosis
the first cause of acquired disability of the young adults

2.5 millions persons with multiple sclerosis worldwide

Heterogenous prevalence : a latitude gradient

In France : 100 000 persons with multiple sclerosis

A disease affecting predominatly women
Sex ratio: 3/1

Age at onset
A disseminated disease of the central nervous system
Inter-individual variability+++ 
Poor prognostic markers

Therapeutic advances +++
With anti-inflammatory strategy

But preventing long term disability progression is still an unmet need
Multiple sclerosis:
an inflammatory, demyelinating and neurodegenerative disease of the central nervous system

- Inflammatory: immune cells infiltration
- Demyelinating: central nervous system myelin
- Neurodegenerative: damage of neurons and axons
- Potentiality for repair: remyelination
Multiple sclerosis: a multifactorial disease

Trigger: viral infection?

Genetic susceptibility

Environment?

central nervous system auto-immunity
MS pathogenesis: a multifactorial disease

Periphery

Activated lymphocyte

Virus + Genetic + Environment

Central nervous system

T and B lymphocytes

MS plaques
demyelination and axonal damage
T lymphocytes in MS

**CD4 T cells**

- Experimental models: auto-immune potential of CD4 (CNS) specific T cells
  - T-helper-1 (Th1) type
  - Thelper -17 (Th17) type

- Rational for most immuno-modulatory therapies in MS

**CD8 T cells**

- Cytotoxic role

- Predominate in MS lesions

*From Hohlfeld et al, 2015*
Regulatory T cells in MS

Defect of efficacy of T regulatory cells in MS

*Viglietta et al, J Exp Med. 2004*

Favouring T regulatory T cells in MS using low doses IL2

MS-IL2 trial : an ongoing phase 2

Academic (PI : D Klatzman and C Lubetzki)

30 relapsing-remitting multiple sclerosis patients

Primary endpoint
  T regulatory cells

Secondary endpoint
  MRI : new lesions
B lymphocytes in multiple sclerosis: the new player

- Neuropathology
  - B lymphocytes in CNS lesions
  - B lymphocytes in meningeal infiltrates
- CSF: oligoclonal bands
- Efficacy of therapy targeting B cells

Ocrelizumab in relapsing remitting MS

Annualized relapse rate

46% ARR reduction vs IFN β-1a
p < 0.0001
Myeloid cells response in multiple sclerosis: a double edge sword?

• Microglia and macrophages are hallmarks of active lesions with ongoing demyelination and axonal injury

• Microglial activation is detected outside the plaques, in the so-called normal appearing white matter

• Microglial activation is associated with disability progression

• But… Suppression of macrophages in experimental models reduces myelin repair
From pathophysiology to therapeutic

Different phases of the disease

- Remitting phase
- Progressive phase
- Inflammation
- Neurodegeneration
From pathophysiology to therapeutic

- **Anti-inflammatory strategies**
  - Reduce relapse rate
  - But insufficient to prevent disability progression

- **Progression of disability in MS is related to accumulation of irreversible axonal/neuronal damage**
  - Partially independent of inflammation
  - Occurring early in disease evolution

**Prevention of neurodegeneration is the major unmet need in MS!**

*Trapp, 1998*
Different types of neurodegeneration: Acute and chronic damage

• Acute axonal injury
  • Mostly inflammation dependant

Trapp and Nave 2008

Courtesy of Bruce Trapp
Different types of neurodegeneration
acute and chronic damage

• Chronic axonal injury
  • Partially independant of inflammation
  • Directly or indirectly dependant of demyelination
Mechanisms of chronic axonal injury

<table>
<thead>
<tr>
<th>Directly related to demyelination</th>
<th>Indirectly related to demyelination: increased vulnerability</th>
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<tr>
<td>• Sodium channels redistribution</td>
<td>• Excitotoxicity</td>
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<td>• Disruption of axon/oligodendrocyte metabolic coupling</td>
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<td>• Increased axonal Ca++</td>
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Axonal domains of myelinated fibers

Sodium channels are aggregated at the node of Ranvier

Charles et al. PNAS 2002
Desmazières et al., Mult Scl 2012
Freeman et al, PNAS 2015
In multiple sclerosis lesions, sodium channels are redistributed along naked axons.

Coman et al, Brain 2006
« adaptative » sodium channels redistribution along naked axons results in axonal damage

Strategy of Nav channels blockade

Lamotrigine in progressive MS (2010)
phase 2
negative

Phenytoine in optic neuritis (2016)
phase 2
positive: 30% protection

Craner et al, PNAS 2004
Mechanisms of chronic axonal injury

Directly related to demyelination

- Sodium channels redistribution
- Disruption of axon/oligodendrocyte metabolic coupling

Indirectly related to demyelination: increased vulnerability

- Excitotoxicity
- Oxidative stress
- Mitochondrial dysfunction
- Increased axonal Ca^{++}
Demyelination disrupts metabolic coupling between oligodendrocyte and axons resulting in axonal « metabolic disease »
Preventing neurodegeneration in MS

Neuroprotective strategy

Remyelination strategy
Neuroprotective strategies: trials ongoing

- Sodium channels redistribution
- Disruption of axon/oligodendrocyte metabolic coupling
- Excitotoxicity
- Oxydative stress
- Mitochondrial dyfunction
- Increased axonal Ca++

Blockers of sodium channels

- Anti-glutamate
- Anti-oxidants, EPO
- Resveratrol?
Preventing neurodegeneration in MS

Neuroprotective strategy

Remyelination strategy
Multiple sclerosis is a disease with repair capacity

- Remyelination occurs in multiple sclerosis
- Remyelination prevents neurodegeneration
- Promoting remyelination to prevent neurodegeneration, hence disability progression
Remyelination strategies in multiple sclerosis

Favoring exogenous repair: grafts

Promoting endogenous repair

Stankoff et al, Current opinion in Neurology 2016
Jadasz et al, Current Opinion in Neurology 2016
Take home message

- In multiple sclerosis, disability progression is due to irreversible axonal/neuronal damage

- Part of neuronal damage is inflammation dependant, hence reduced by anti-inflammatory drugs

- Part of neuronal damage is independent of inflammation, and related to demyelination

- Strategies to prevent neurodegeneration are actively developed
  - Remyelination trials
  - Neuroprotective trials

Now at bedside