The importance of barriers in multiple sclerosis

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Multiple sclerosis (MS)

- A chronic auto-immune disease that damages the central nervous system
- Destruction of myelin and associated tissues
- Causes severe physical and cognitive disabilities
- > 2 million patients world-wide
- No treatments completely stop the progression of the disease
What causes multiple sclerosis?

**Etiology of MS**

- **Causes**: undetermined and multifactorial

- **Disease penetrance**: Stochastic events and environmental factors in genetically susceptible individuals

- **Genetic factors**: 30-40% risk to develop MS in concordant twins

**Immunological mechanistic of disease triggering:**

- **CNS extrinsic model**:
  - Autoractive T cells activated at peripheral sites
  - Activated autoreactive T cells traffic to the CNS together with activated B cells and monocytes

- **CNS intrinsic model**:
  - CNS intrinsic events trigger the disease development
  - Infiltration of autoreactive T cells as a secondary phenomenon
Immune system dysregulation outside of the central nervous system
Neuroanatomy of the vascular blood–brain barrier (BBB)

Shechter et al, Nat rev, 2013

The blood brain barrier (BBB): a protective barrier

Pinheiro et al, Biochimica et Biophysica Acta, 2016
The blood brain barrier (BBB): a protective barrier
Alteration of BBB in multiple sclerosis

Bradl et al, Seminars in Immunopathology, 2009
Different clinical forms of MS

Relapsing-remitting MS

85%
CNS inflammation in RRMS

Dendrou et al. Nat Rev, 2015
Inflammation in the CNS leads to an upregulation of trafficking molecules on the BBB.
Opened BBB in RRMS

Bradl et al, Seminars in Immunopathology, 2009
Inflammatory activity in RRMS

Rovira et al, Ther Adv Neurol Disord, 2013
What are the immune cells involved in RRMS phase?
Multiple Sclerosis: a **CD4 T cell** mediated disease

**Human**

- **GWAS studies**: association of CD4 T cell loci, including MHCII alleles, with disease susceptibility
- **Activated myelin antigen specific CD4 T cells** in MS patients
- **Alteration of CD4 T cell subsets** in MS patients (**Th17, Th1, Treg**)

**Mouse model**

- **EAE induction**: dependent on myelin-specific CD4 T cells (immunization with myelin Ag, transfer of activated T cells isolated from animal immunized w/ myelin Ag, myelin specific Tg TCR)
- **Mice deficient in CD4 T cells are resistant to EAE induction**, susceptibility restored by the transfer or induction of CD4+ T cells
B cells in Multiple sclerosis (1960-2008)

Discovery of intrathecally synthesized oligoclonal IgG bands (OCB) in CSF of MS patients: indicates clonal expansion of B cells in the CSF

- Present in >90% of MS patients
- BUT: not specific of MS, undetermined antigen-specificity, unclear pathogenic role

⇒ Indicates abnormal B cell activation within the CNS
⇒ Diagnostic criteria for MS
B cells in Multiple sclerosis (2008-.....)

2008

B-Cell Depletion with Rituximab in Relapsing–Remitting Multiple Sclerosis

B cell depletion (CD20 antibody) reduces symptoms of RRMS

=> Role of B cells in MS pathogenesis?

- Antibody dependent?
- No change in OCB

- Antibody independent?
- APC
  - Bystander effect
  - Regulatory role
  ...

The NEw ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

B-Cell Depletion with Rituximab in Relapsing–Remitting Multiple Sclerosis

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and Craig H. Smith, M.D., for the HERMES Trial Group®
Plus other immune cell types....
Therapeutic approaches in RRMS

Martin et al, EJI, 2016
Secondary progressive Multiple Sclerosis (SPMS)

- Physical disability: 85%
- 10 years post MS-onset: 50%
- 20 years post MS-onset: 90%

Several therapeutic options

NO effective treatments
Recent paradigm shift in MS: Association of grey matter lesions with progression

Long believed to be “white matter disease”

- Grey matter lesions are much more common than initially anticipated
- Grey matter lesions are associated with disease progression (Magliozzi et al. Brain 2007; Rudick et al. NEJM, 2009)

Dendrou et al. Nat Rev, 2015
SPMS: meningeal inflammation behind a closed BBB

Bradl et al, Seminars in Immunopathology, 2009
Ectopic GCs in SPMS

• **Lymphoid like structure**: antibody generation, affinity maturation, class switching, clonal expansion of B cells

• Present in 40-54% of SPMS patients

• Almost exclusively found adjacent to large subpial lesions

• Associated to an increased severity of pathological changes and clinical manifestations of the disease

• **Gradient of neuronal loss** suggesting that soluble factors diffusing from these structures have a pathogenic role

*Calabrese et al, Nature Rev Neurosci, 2015*
Meningeal B-cell follicle-like structures in SPMS patients

Ectopic germinal centers

Inflammatory cell infiltrates

Magliozzi et al. Brain, 2007
Immune-mediated mechanisms of subpial cortical demyelination in progressive multiple sclerosis

Calabrese et al. Nat rev neurosciences, 2015
Gradient of neuronal loss in follicle positive SPMS patients
Different clinical forms of MS and...

- Opened or closed blood-brain barrier
- Different immune mechanisms
- Different types of brain lesions

Different therapeutic approaches
Intestinal barrier: another barrier of interest in Multiple Sclerosis?
Microbiota, intestinal barrier and gut immune system

Hand et al,
Trends in Immunology, 2016
The mucosal layer represents the major immune interface with the environment

**Environment**
- Pathogens,
- Chemicals,
- Diet,
- Sun exposure,
- Smoking

- Nasal mucosa
- Tonsil
- Oral mucosa
- Tracheal mucosa
- Respiratory mucosa
- Skin
- Gastric mucosa
- Intestinal mucosa
- Payer’s patches

=> largest mucosal surface

=> 70% of our immune cells reside in the GI tract
Role of the gut microbiota in autoimmune diseases

Kamada et al, Nat. Rev, 2013
The microbiota-gut-brain axis

Crosstalk between the microbiota, immune system and CNS: Metabolic, endocrine, neural and immune pathways

- **Microbe-derived molecules**
  - SCFAs (microglia maturation and function)
  - Tryptophan metabolites, AHR ligands (astrocyte function)
  - MAMPs (LPS, PGN)

- **Neuroactive molecules**
  - Intestinal neurotransmitter biosynthesis
  - Regulation of neurotransmitter signaling

- **Neuronal signaling**
  - Vagal nerve stimulation

- **Tissue inflammation, injury and repair**
  - $T_{H1}$ (IFN$\gamma$), $T_{H2}$ (IL-4), $T_{H17}$ (IL-17A), $T_{reg}$ (IL-10)

- **Neurogenesis**
  - Ly6C$^+$ monocytes

- **Neural development and connectivity**
  - IL-17A (cortical development)
  - IFN$\gamma$ (neural connectivity)

**Environmental factors**

- **Gut microbiota**
  - SCFAs
  - MAMPs (PSA, TLR and NLR ligands)

- **Immune pathways impacted**
  - $T_{reg}$ differentiation
  - $T_{H17}$ differentiation
  - Antibody production
  - Antigen presentation
  - Mononuclear phagocyte function

Fung et al, Nat Neurosci, 2017
Gut microbiota and Multiple Sclerosis

Dysbiosis in MS patients
Increased intestinal permeability
Differences in Firmicutes, Bacteroidetes and Proteobacteria

Attenuated EAE
↓ IFNg and IL-17 expression by CD4 T cells
↑ Treg

Restored susceptibility to EAE
↑ IL-17+ CD4 T cells

Attenuated EAE
↑ IL-10+ Treg

Germ-free + SFB (Segmentous filamentous bacteria)
Germ-free + PSA (Bacteroides fragilis)

Lee et al, PNAS, 2011
Ochoa-Reparaz et al, Mucosal Immunol, 2010
Buscarinu et al, Neurotherapeutics, 2018
Fung et al, Nat Neurosci, 2017
Migration of gut CD4 T cells to target organs in autoimmune disease

EAE
Microbiota composition induces pathogenic CD4 T cells in the brain

Autoimmune arthritis
Egress of Peyer’s path TFh to systemic lymphoid tissues
=> Arthritis exacerbation

Glomerulonephritis
Intestinal Th17 migrate to inflamed kidney
=> Aggravation of the disease

Teng et al, Immunity, 2016
Krebs et al, Immunity, 2016
Gut microbiota in MS

Beneficial & harmful bacteria (animal model)

The international MS microbiome study

http://imsms.org
Different clinical forms of MS and...

- Opened or closed blood-brain barrier
- Microbiota
- Different immune mechanisms
- Different types of brain lesions
- Microbiota

Different therapeutic approaches