

Multiple sclerosis – immunology

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Learning objectives

Understanding the basis for implicating the immune system in the pathogenesis of MS

Describing the key cells and trafficking pathways implicated in CNS inflammation in MS

Discussing the relationship between inflammation and neurodegeneration

MS pathogenesis – the working hypothesis

- MS is primarily considered an **inflammatory**, probably **autoimmune** demyelinating disease of the CNS, widely held as being initiated by **T and B lymphocytes**
- A **neurodegenerative component** to the disease is increasingly recognised
- Exact cause of the pathological process remains unknown

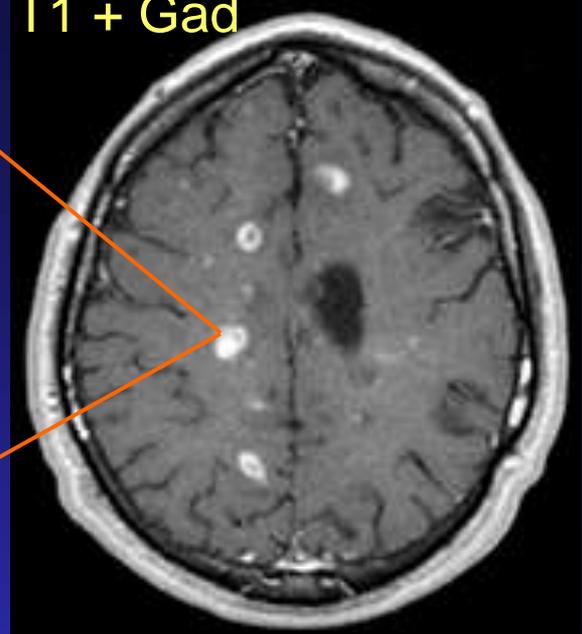
Inflammation and demyelination



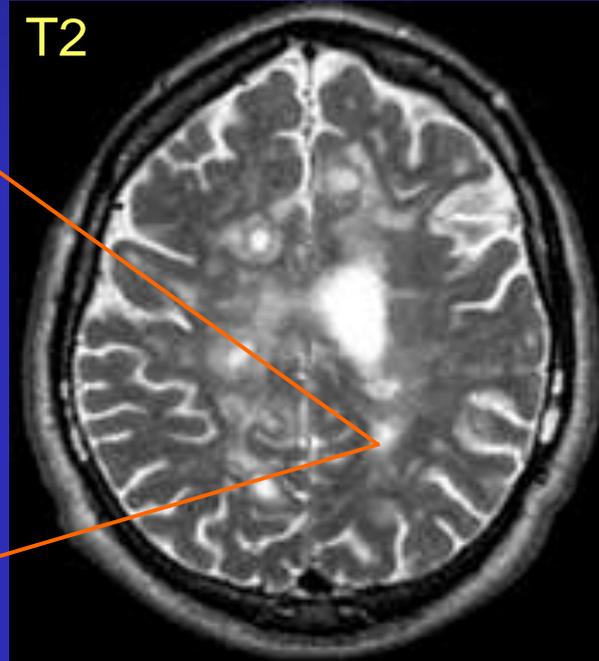
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MRI

T1 + Gad



T2



Axonal damage, gliosis



Trapp et al. NEJM 1998

Basis of the autoimmune hypothesis in MS

- 1. Immunopathology of lesions**
- 2. Susceptibility associated with immune response genes**
- 3. CSF immunological abnormalities**
- 4. Subtle alteration of blood T cell functions**
- 5. Animal models of autoimmune disease**
- 6. Comorbidity and similarities with other autoimmune diseases**
- 7. Response to immuno-suppressive and -modulatory therapies**

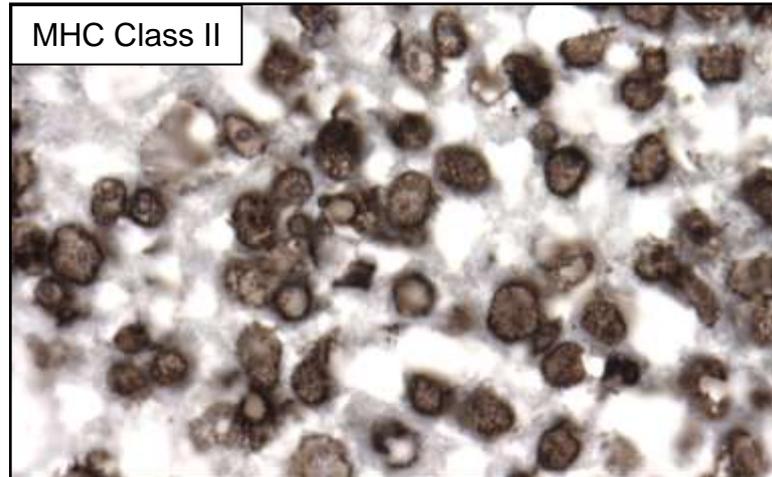
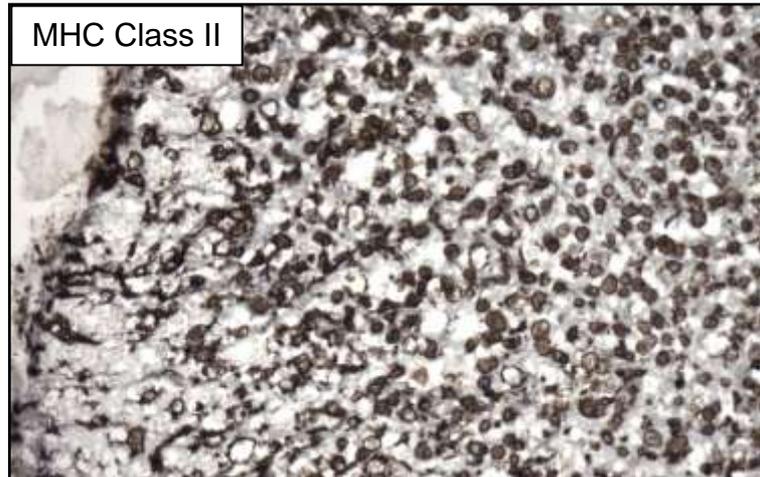
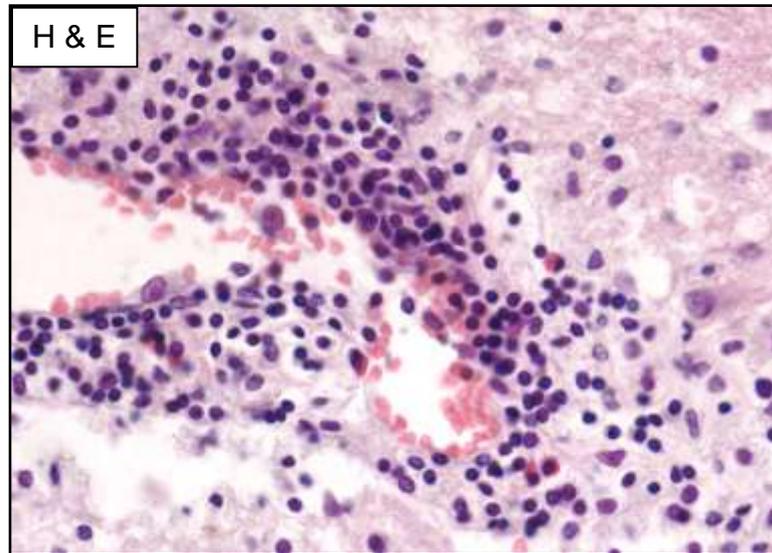
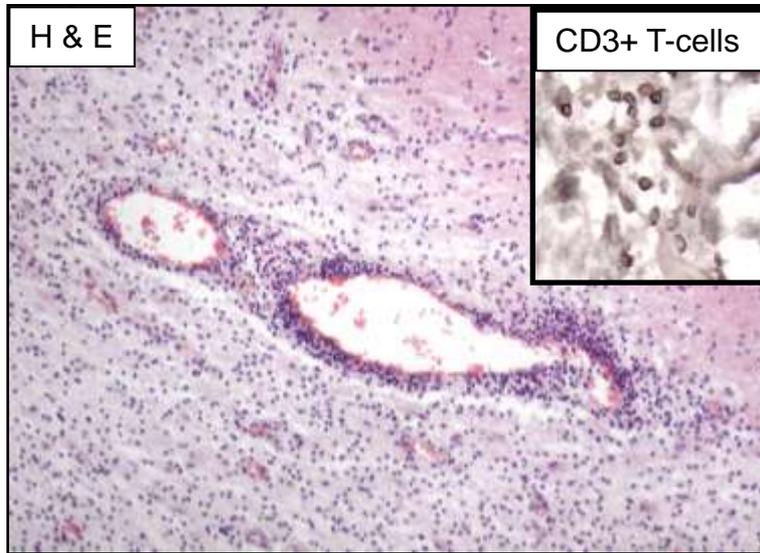
1. Immunopathology of CNS

Perivascular cuffs and intra-parenchymal infiltrates of inflammatory cells, mostly **CD4+** and **CD8+ T cells**

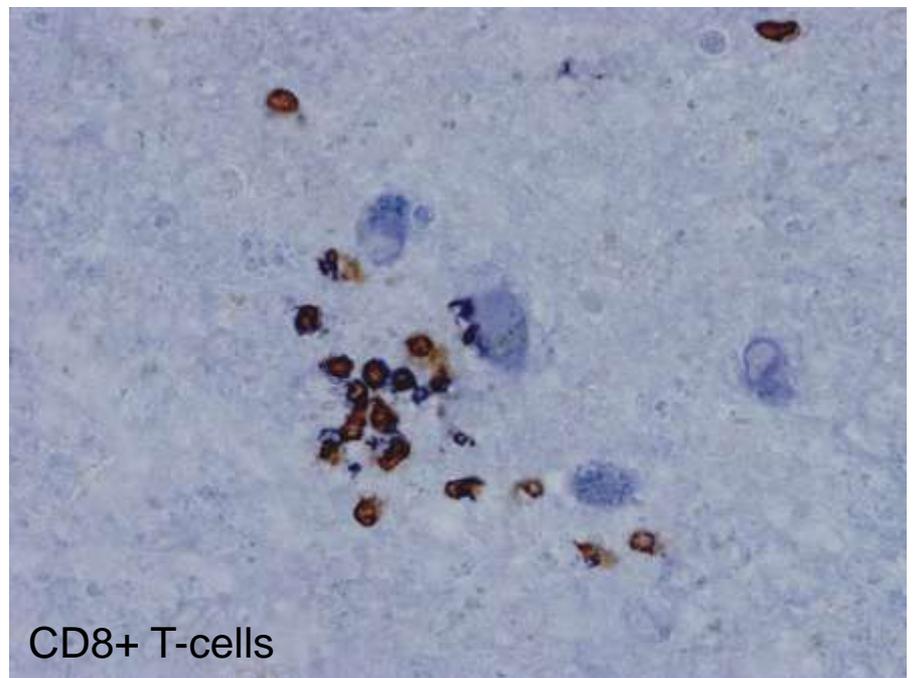
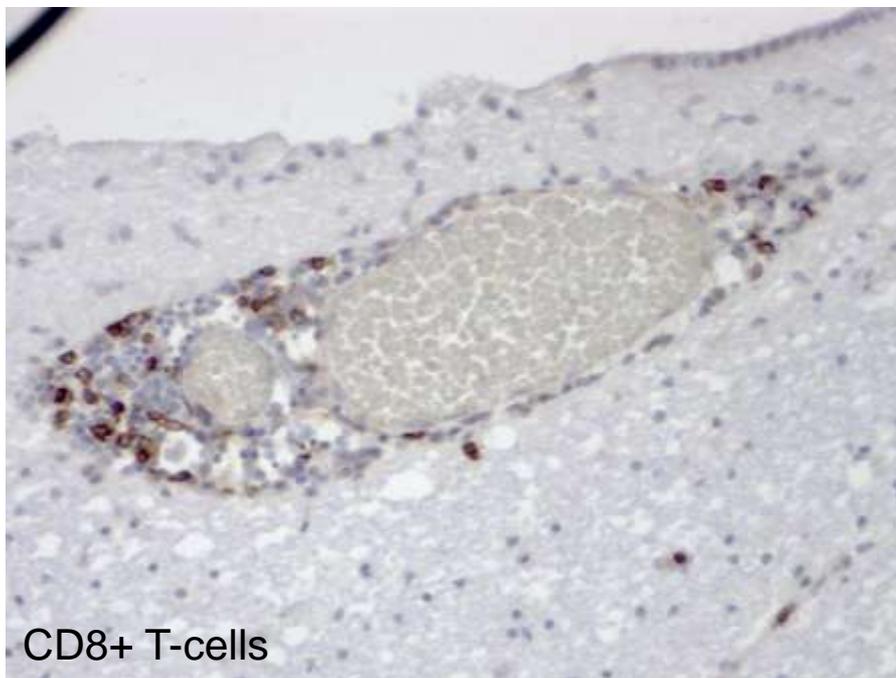
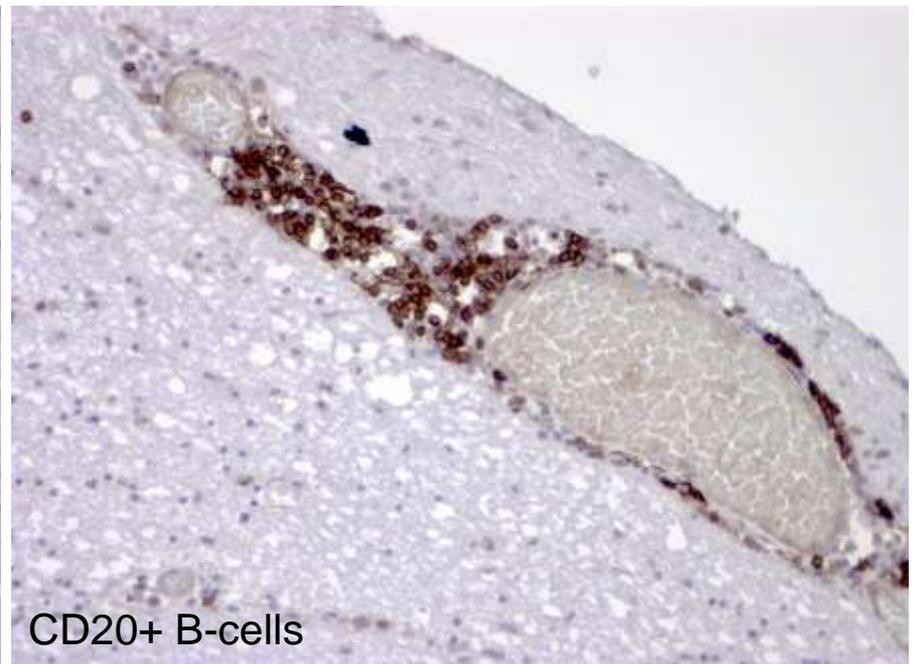
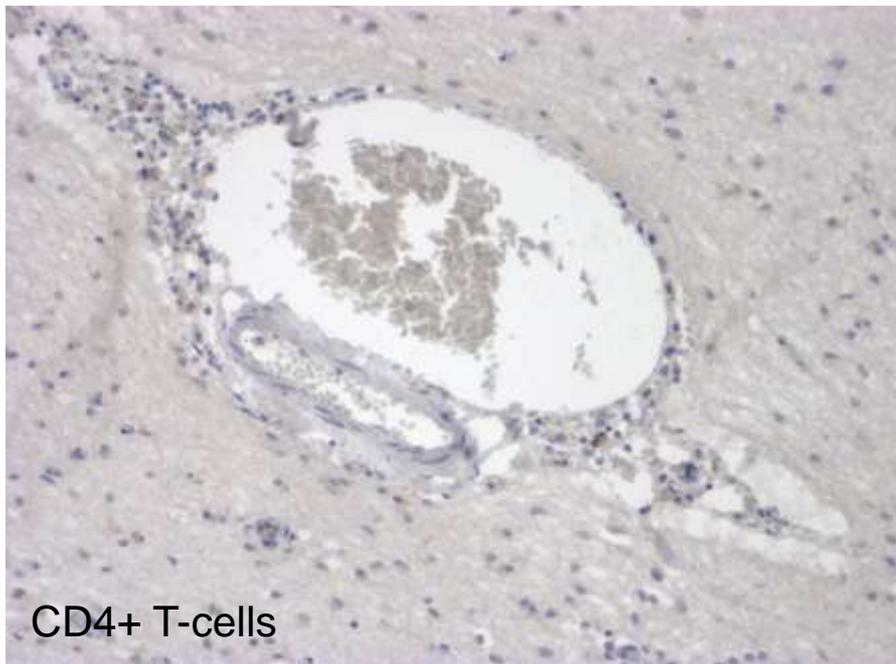
B-cells are found in perivascular and meningeal locations where they can aggregate or form part of ectopic lymphoid follicles

Myelin-laden **macrophages** in and around lesions

Inflammation and MS - the earliest events



T-lymphocyte infiltration is only seen during the very early stages of lesion formation and even during active demyelination (above) only few T-cells are found in the brain parenchyma. B-lymphocytes may also be found in small numbers. The majority of inflammatory cells in the MS lesion are monocytes/macrophages.

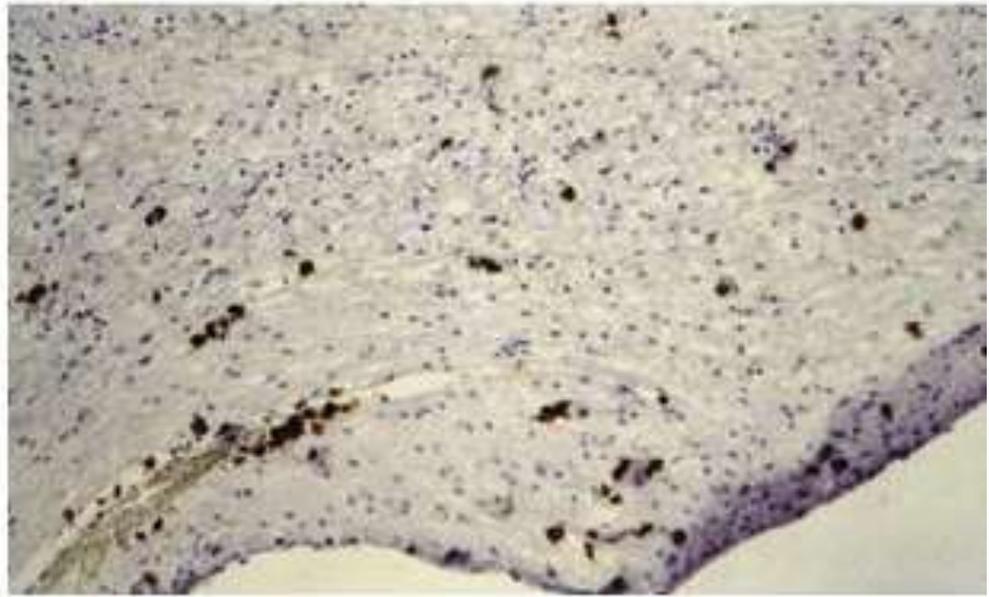
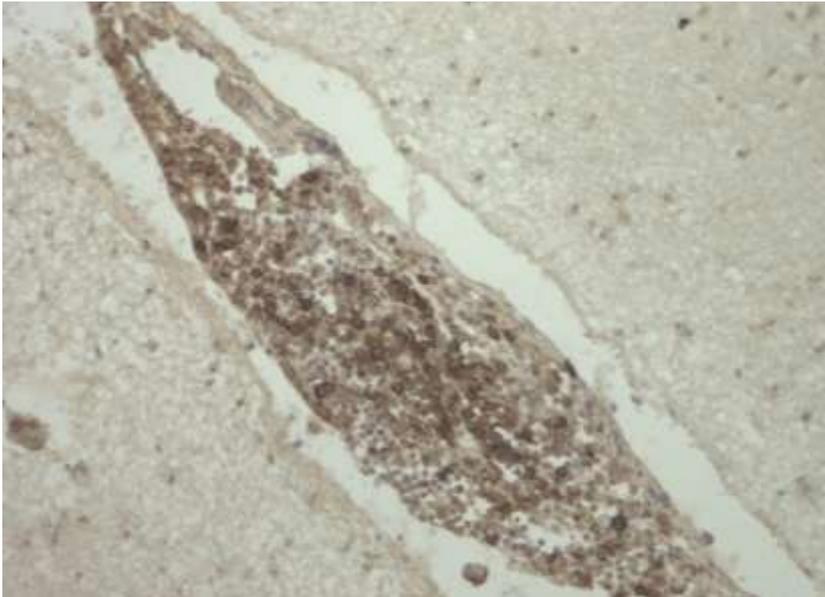


B-lymphocytes and plasma cells

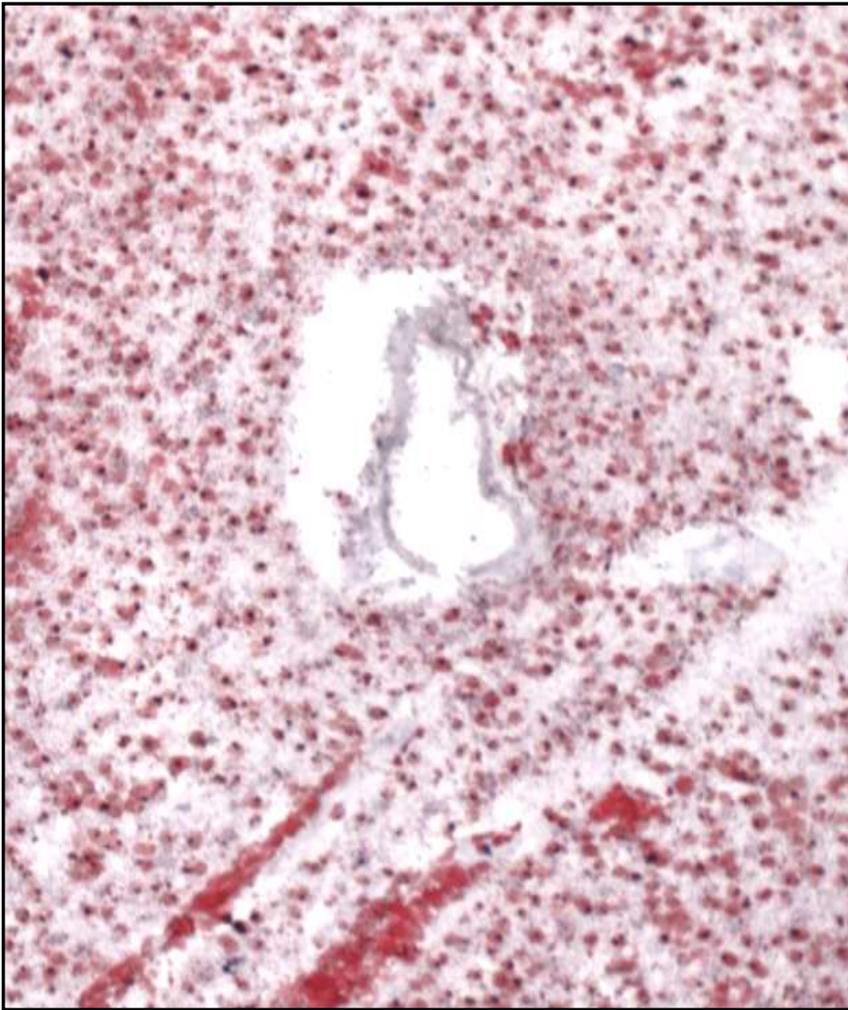


B-cell follicles are found in perivascular and meningeal locations

Isolated B-cells and plasma cells are found in the parenchyma in active lesions and in a perivascular location in chronic lesions



Macrophages and MS

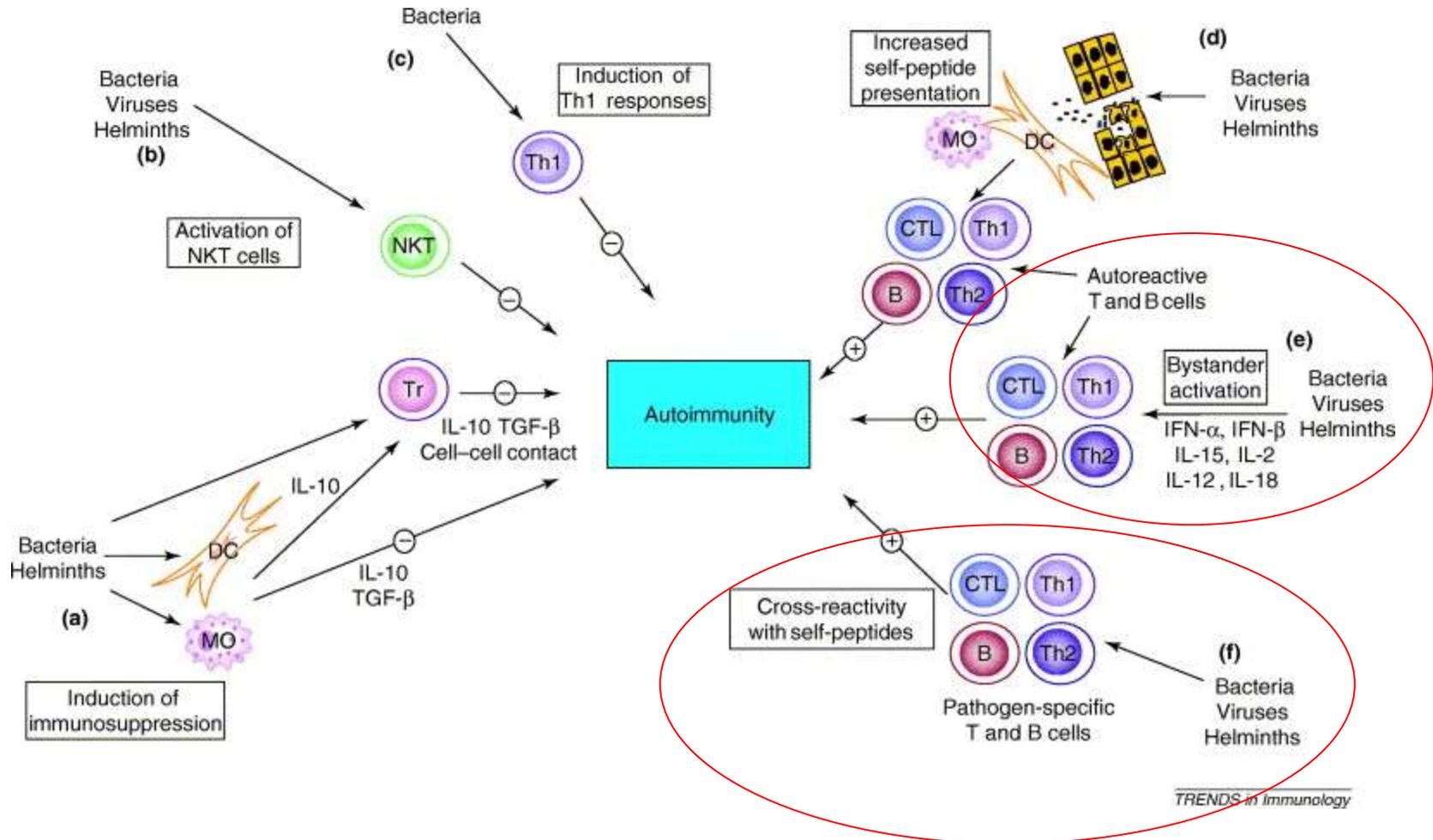


Macrophages in an active MS plaque. The foamy macrophages contain numerous lipid droplets, stained here with oil red-O, which represent myelin breakdown products

How do immune cells become activated?

- To migrate into tissues, including CNS, lymphocytes require activation
- **The events leading to pathological immune activation in MS are unclear**
- Possible mechanisms induce infection or cross-reactivity with microbial, especially viral antigen(s)

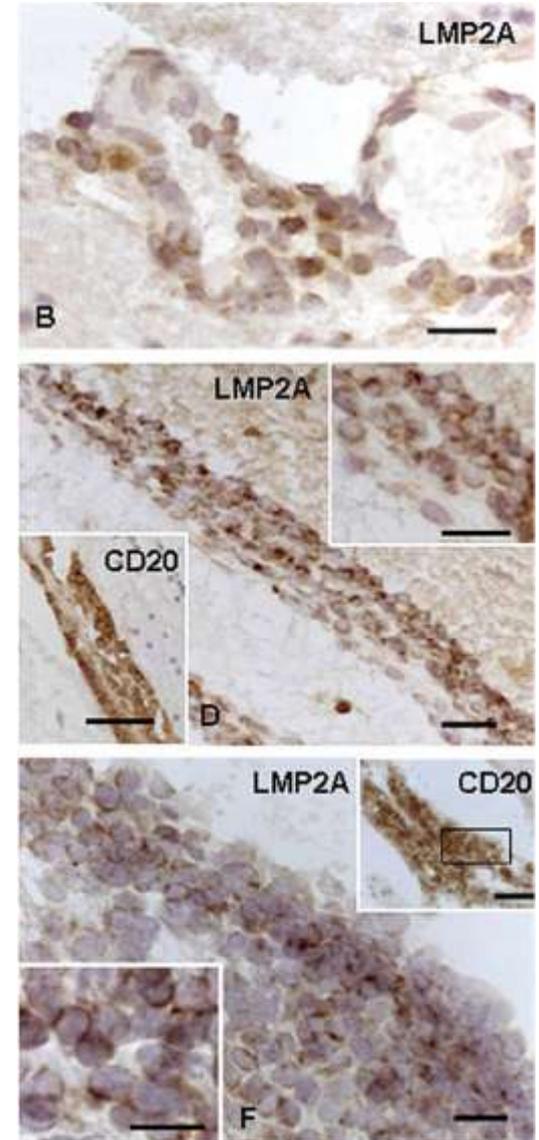
Potential mechanisms for how infections with pathogens might influence the development of autoimmunity



A possible role of EBV in MS pathogenesis:

1 – histological studies

- EBV almost exclusively infects B cells and uses the B-cell differentiation program to establish a persistent, usually asymptomatic, latent infection in humans.
- Using in situ hybridisation and immunohistochemistry, B cells infected with EBV were detected in post-mortem brain tissue (Serafini et al JEM 2007; JNEN 2010)
controversial



A possible role of EBV in MS pathogenesis:

2 – epidemiological studies

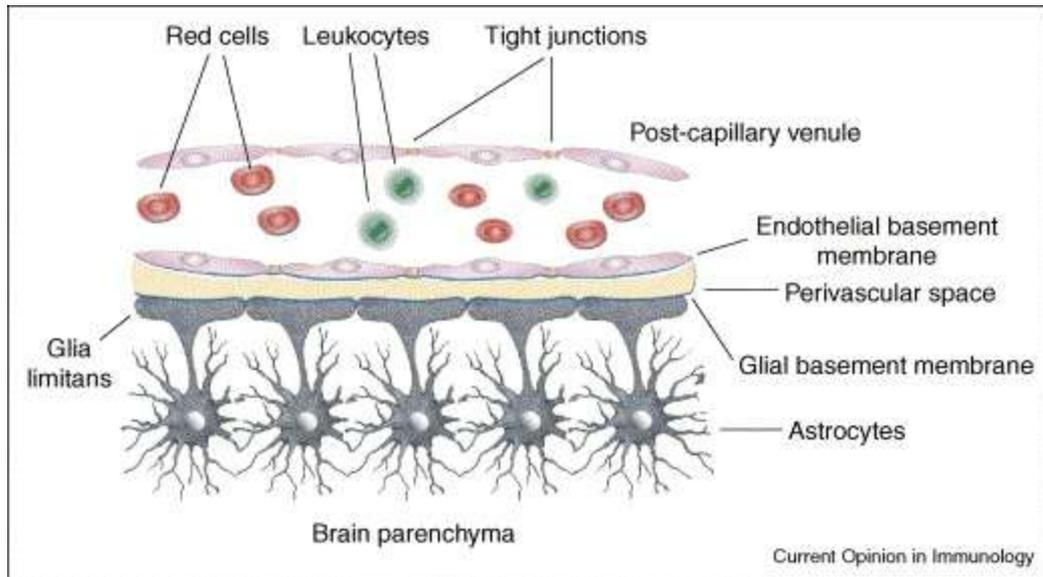
- Large serological studies show ~100% serological positivity for EBV infection in MS vs. 90% in healthy (Ascherio and Munch, *Epidemiology*. 11(2):220-224, March 2000)
- Odds ratio of MS comparing EBV seropositive individuals with EBV seronegative individuals was 13.5 (95% CI = 6.3–31.4)
- In longitudinally followed US military personnel, MS risk was 36-fold higher among individuals with anti-EBNA complex IgG titers ≥ 320 than among those with titers < 20 (Munger et al. *Multiple Sclerosis* 2011)

How do immune cells get to the CNS?

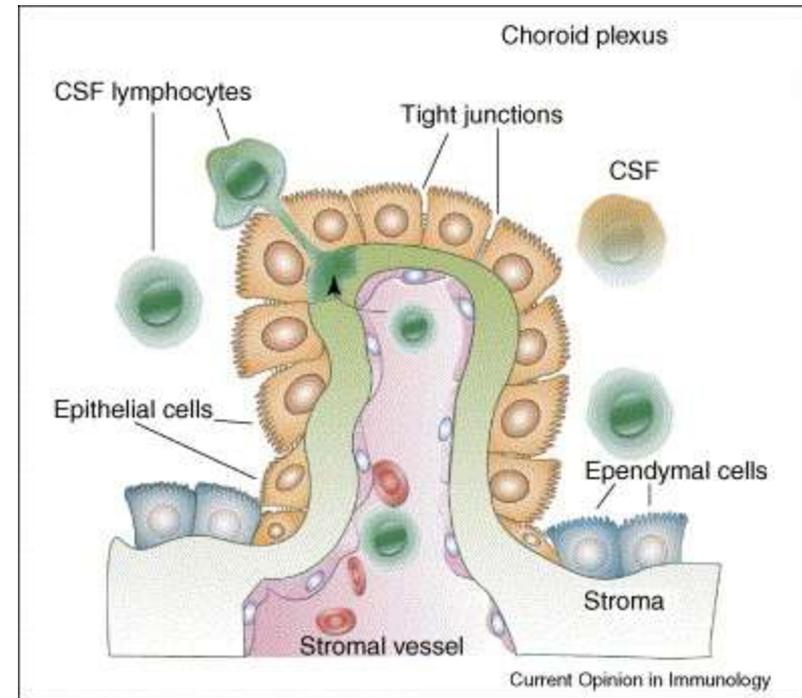
- The CNS is an immune privileged compartment, which is carefully shielded from potentially harmful immune reactions
- There is not a classic lymphatic drainage of the parenchyma
- To get to the CNS leukocytes must pass either of the two physiological barriers:
 1. **The Blood-Brain Barrier**
 2. **The Blood-CSF barrier**

Physiological barriers shielding the CNS

The Blood-Brain Barrier



The Blood-CSF Barrier



Virchow-Robin space

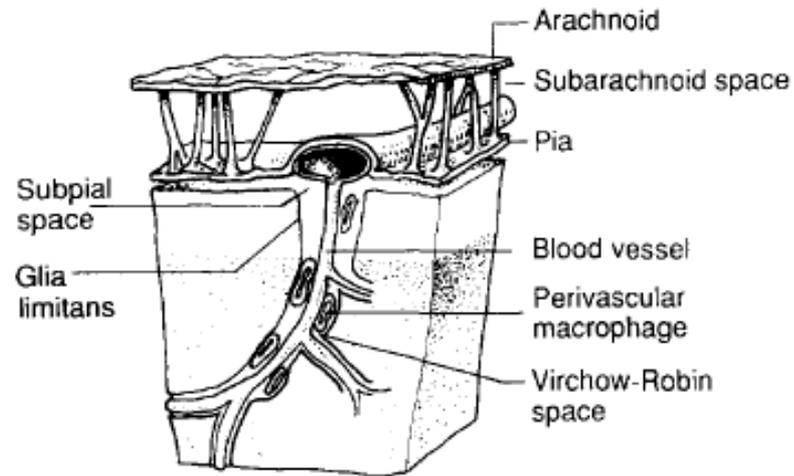


Fig. 1. Diagram illustrating the relationship of the Virchow-Robin space to the subpial and subarachnoid space.

The Virchow-Robin space as an immunological space

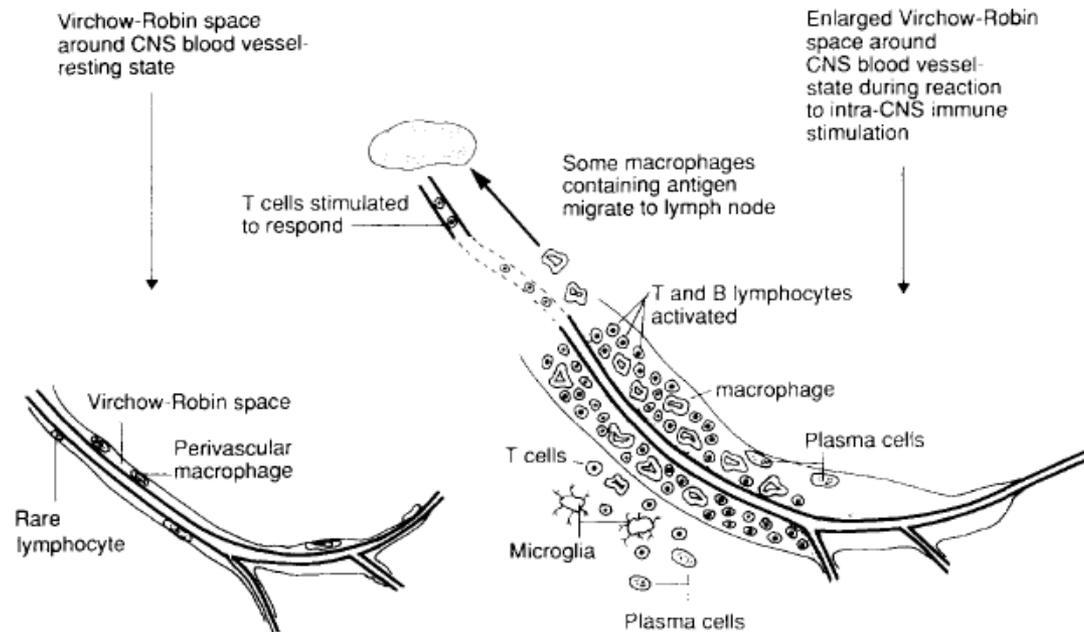
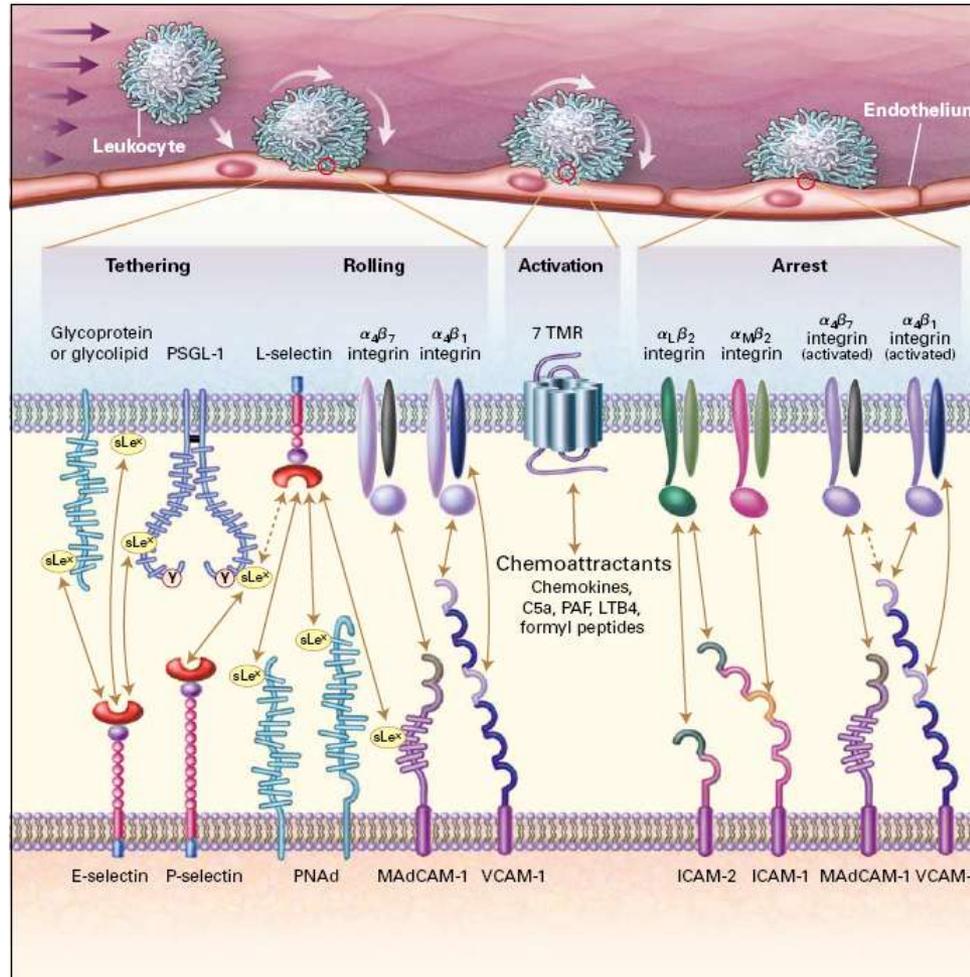
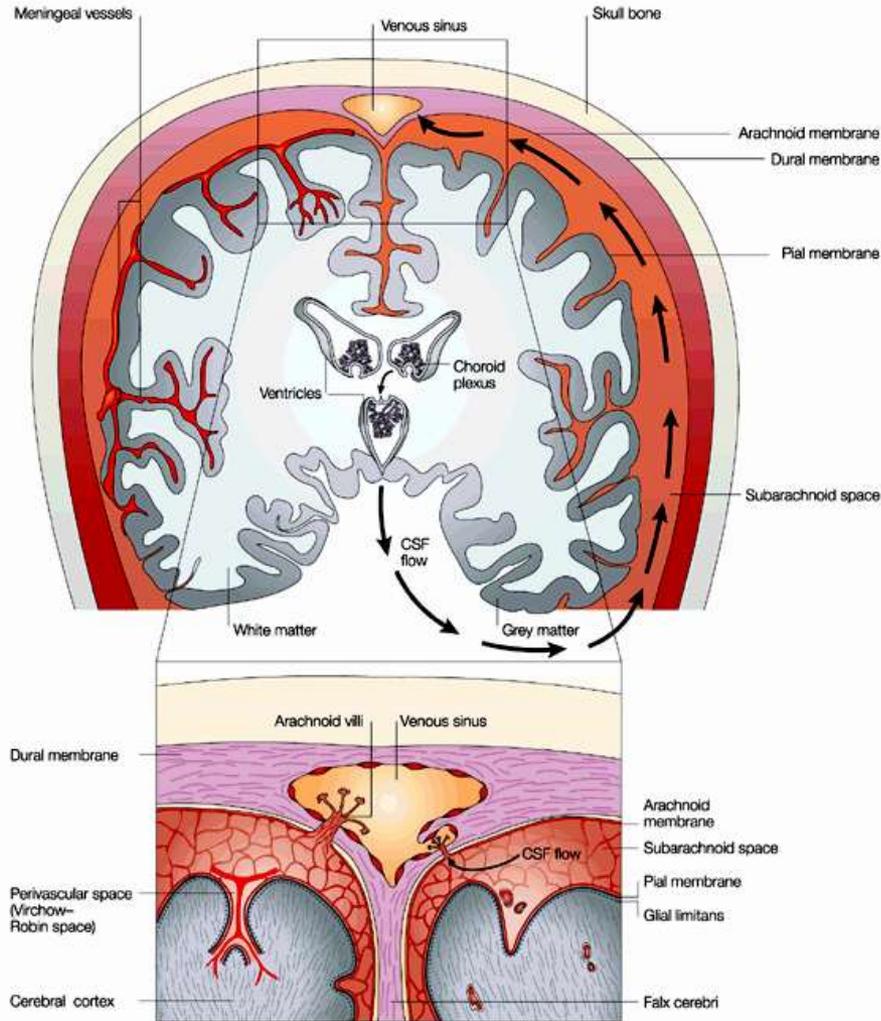


Fig. 2. Diagram illustrating the view put forward here that the Virchow-Robin space is an immunological space that can become expanded and filled with immune competent cells interacting together under conditions of immune stimulation in the brain.

Essential Molecular Players in the Multistep Adhesion Cascade.



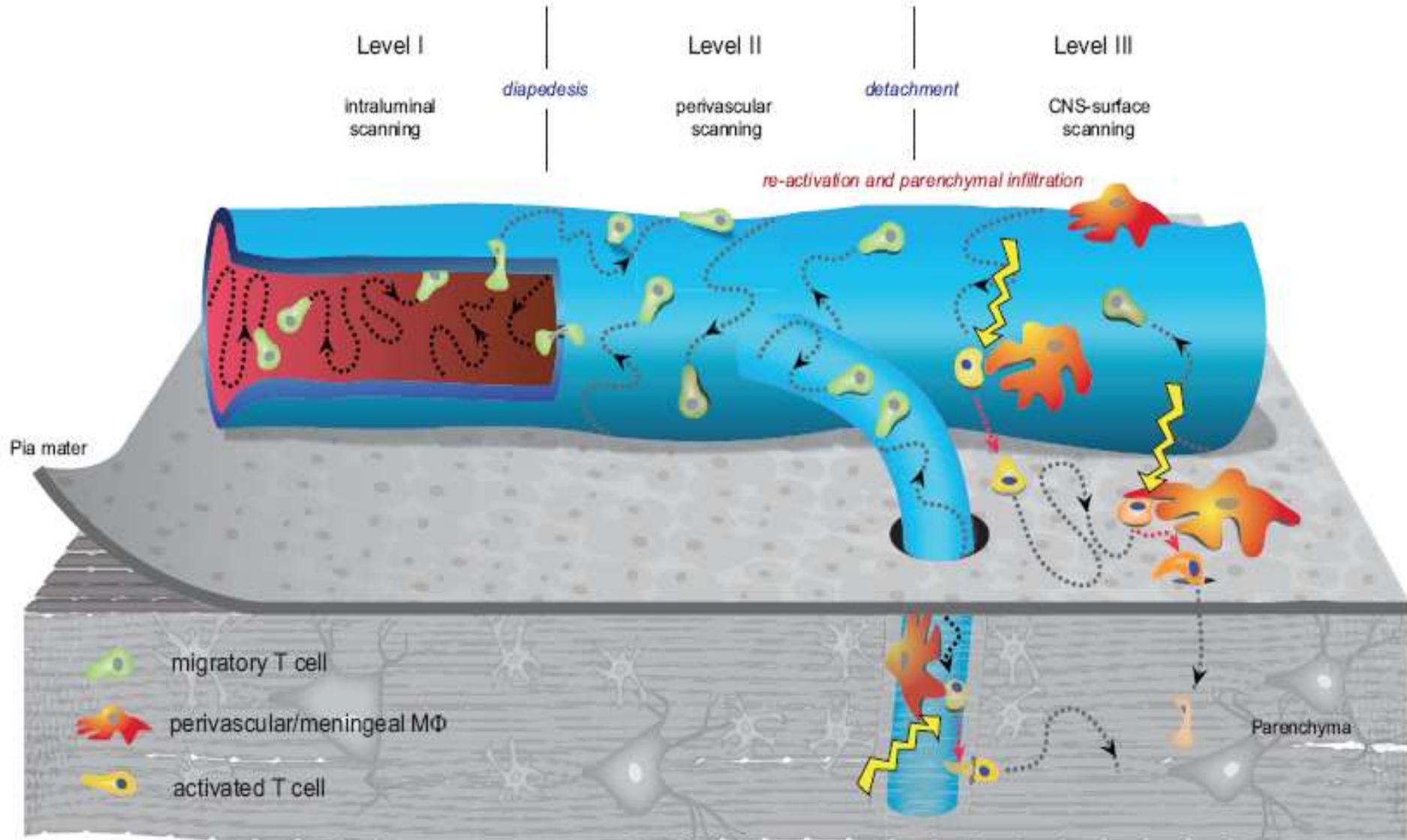
The blood-CSF route to the CNS



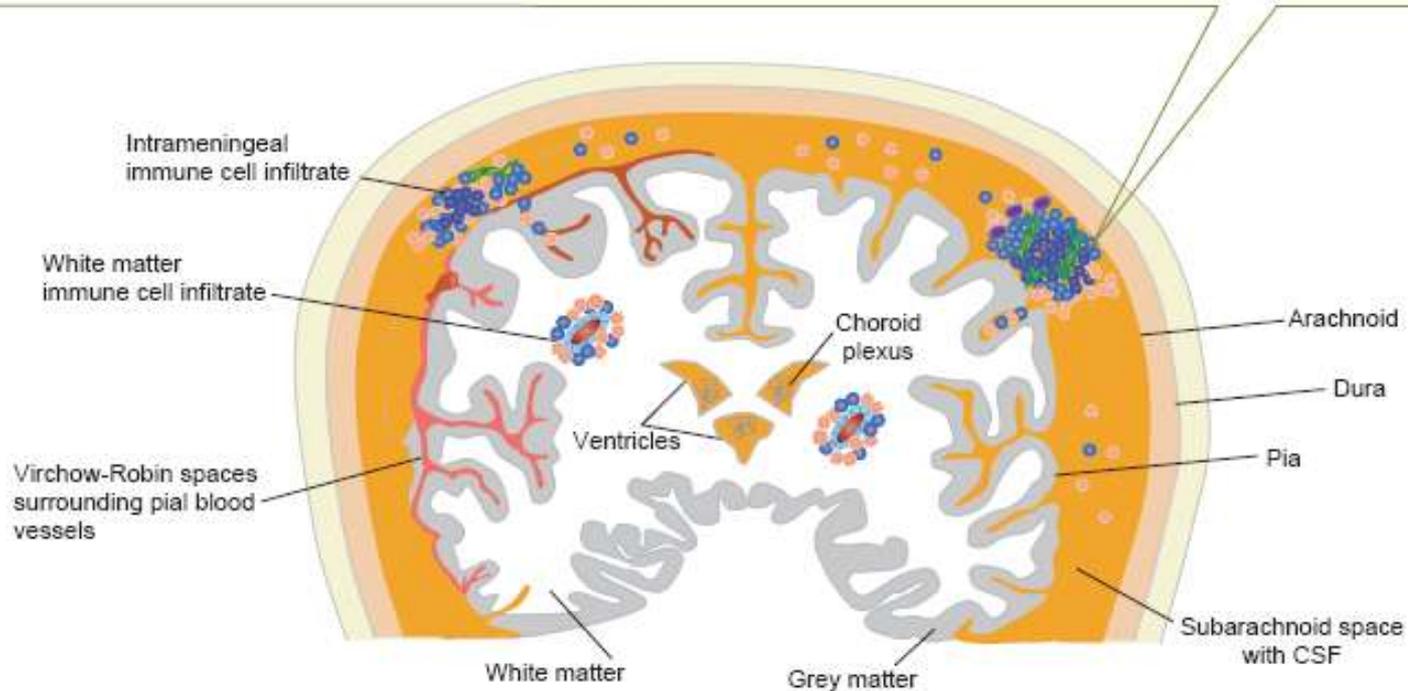
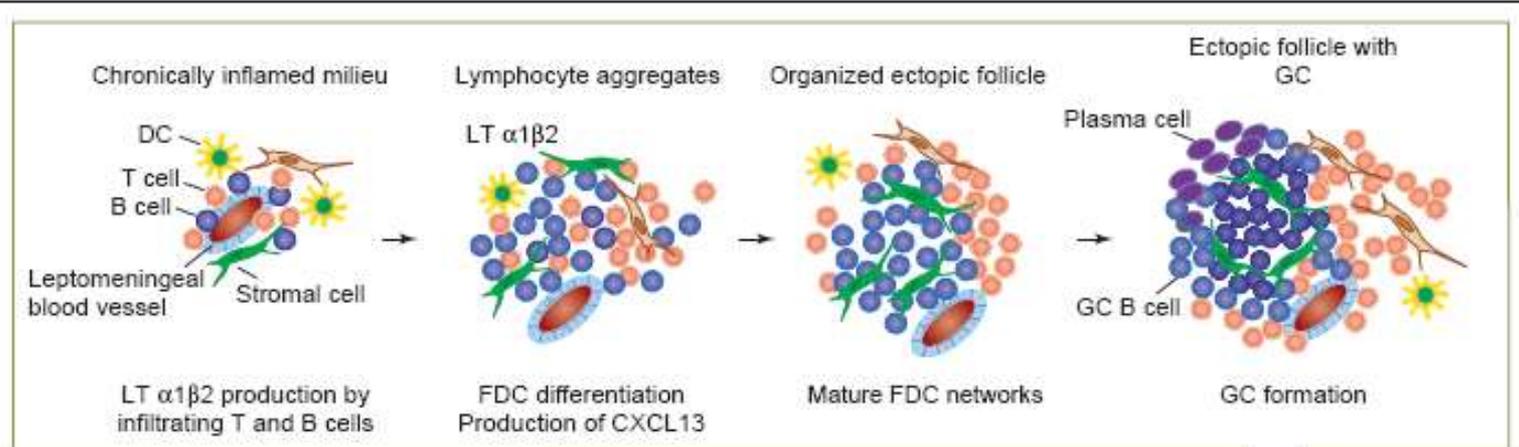
- Choroid plexus
- Subarachnoid space
- Pia
- Brain cortex



Invasion steps of encephalitogenic T cells into their target organ



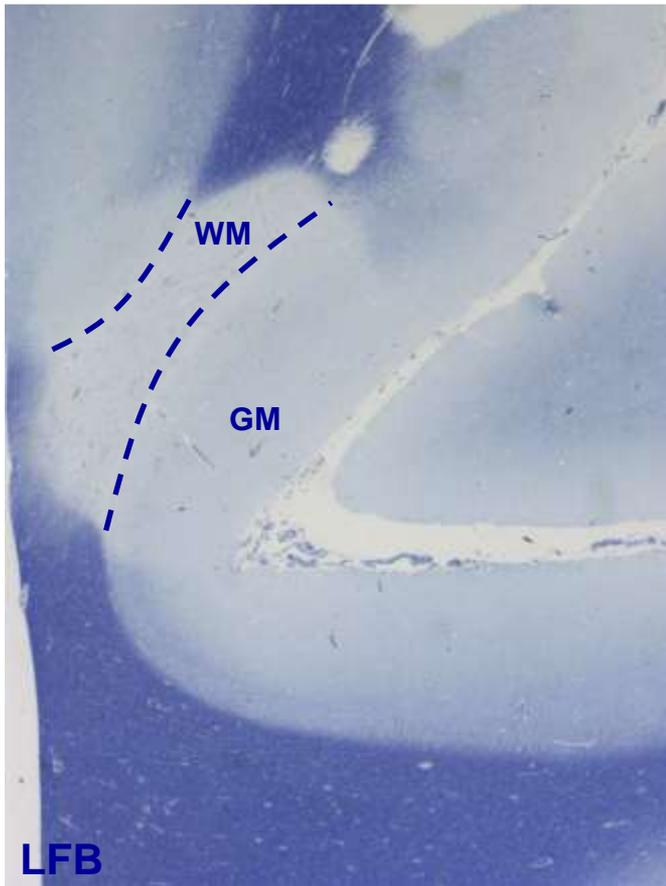
A role for B-cells in cortical pathology



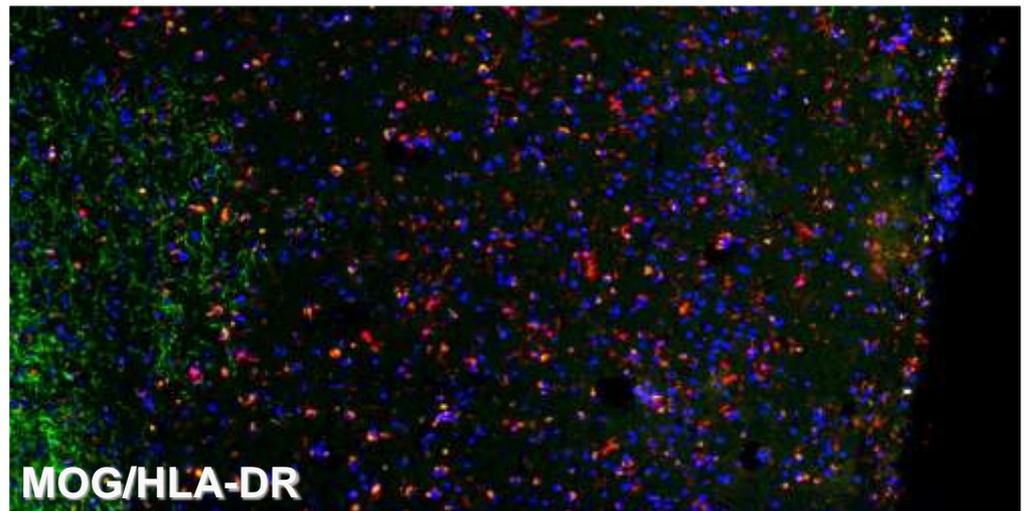
B cell involvement in MS

- In MS lesions (and CSF) there are clonally expanded B cells
- **Ectopic B cell follicles develop in meninges of patients with SP-MS**
- BAFF (B cell activating factor, also named BLyS), a member of the TNF family, is overexpressed in MS tissue (astrocytes)
- Subpial B cell follicles can restimulate inflammatory T and B cells
- Secretion of inflammatory mediators diffusing to the brain cortex

Pathology of grey matter lesions



Grey matter lesions are best identified using myelin protein immunostaining



2. Susceptibility associated with immune response genes

- Whole genome scans in large populations have confirmed associations with immune genes, including:

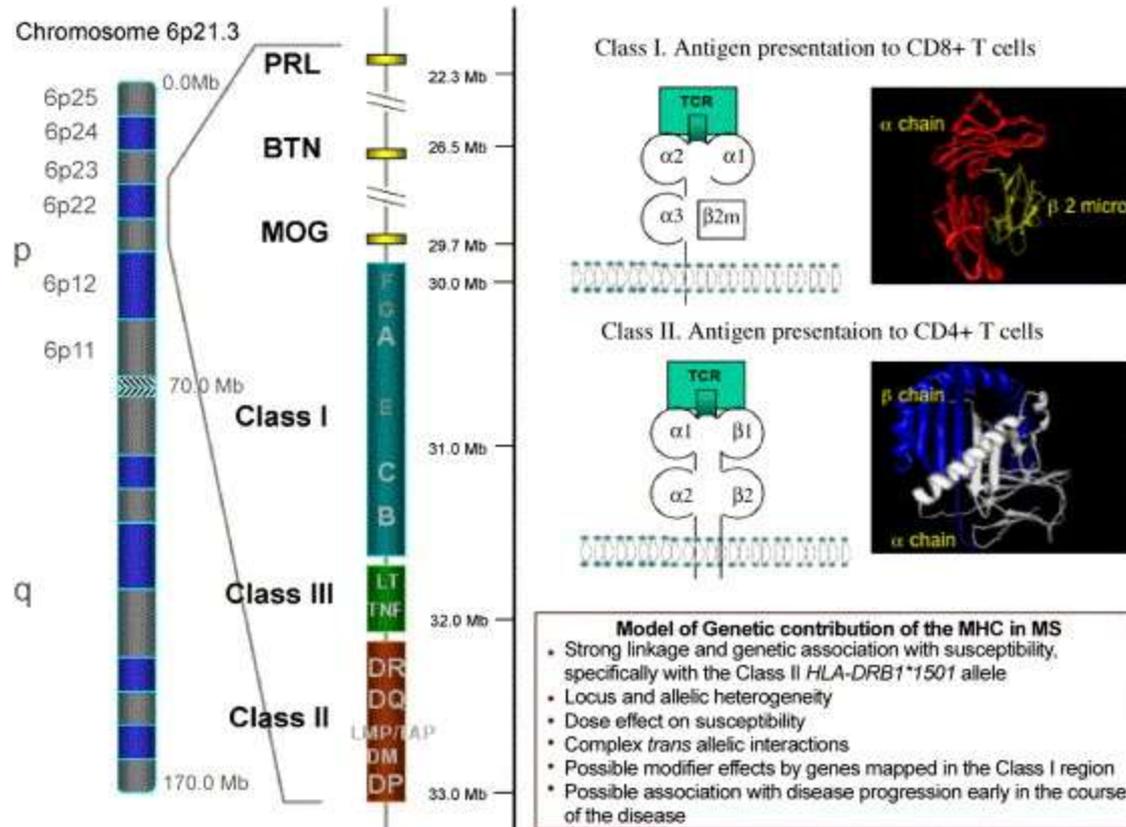
HLA-class II (DRB1*1501, DRB5*0101; DQw6) strongest

IL-7R

IL-2 R alpha

CD58

The 6p21-23 Chromosomal Region and MS



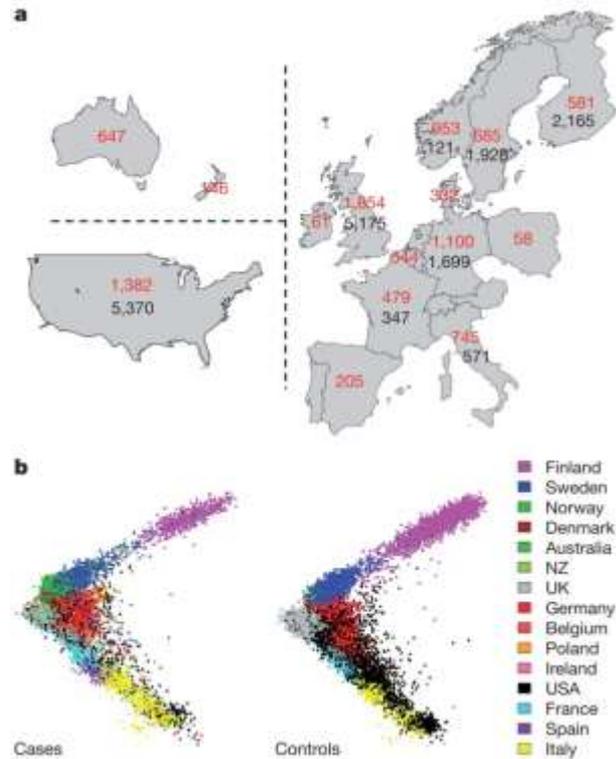
Hauser and Oksenberg, Neuron 2006

Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis

The International Multiple Sclerosis Genetics Consortium* & the Wellcome Trust Case Control Consortium 2*

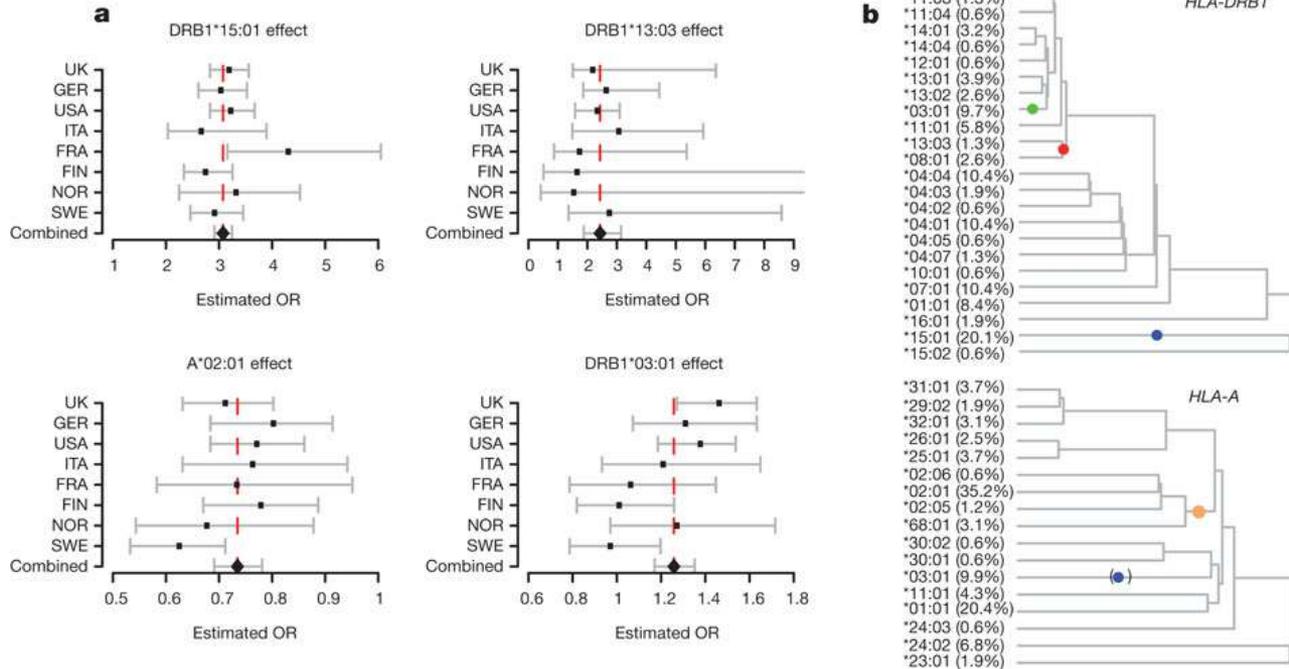
collaborative GWAS involving 9,772 cases of European descent collected by 23 research groups working in 15 different countries

Distribution of cases and controls.



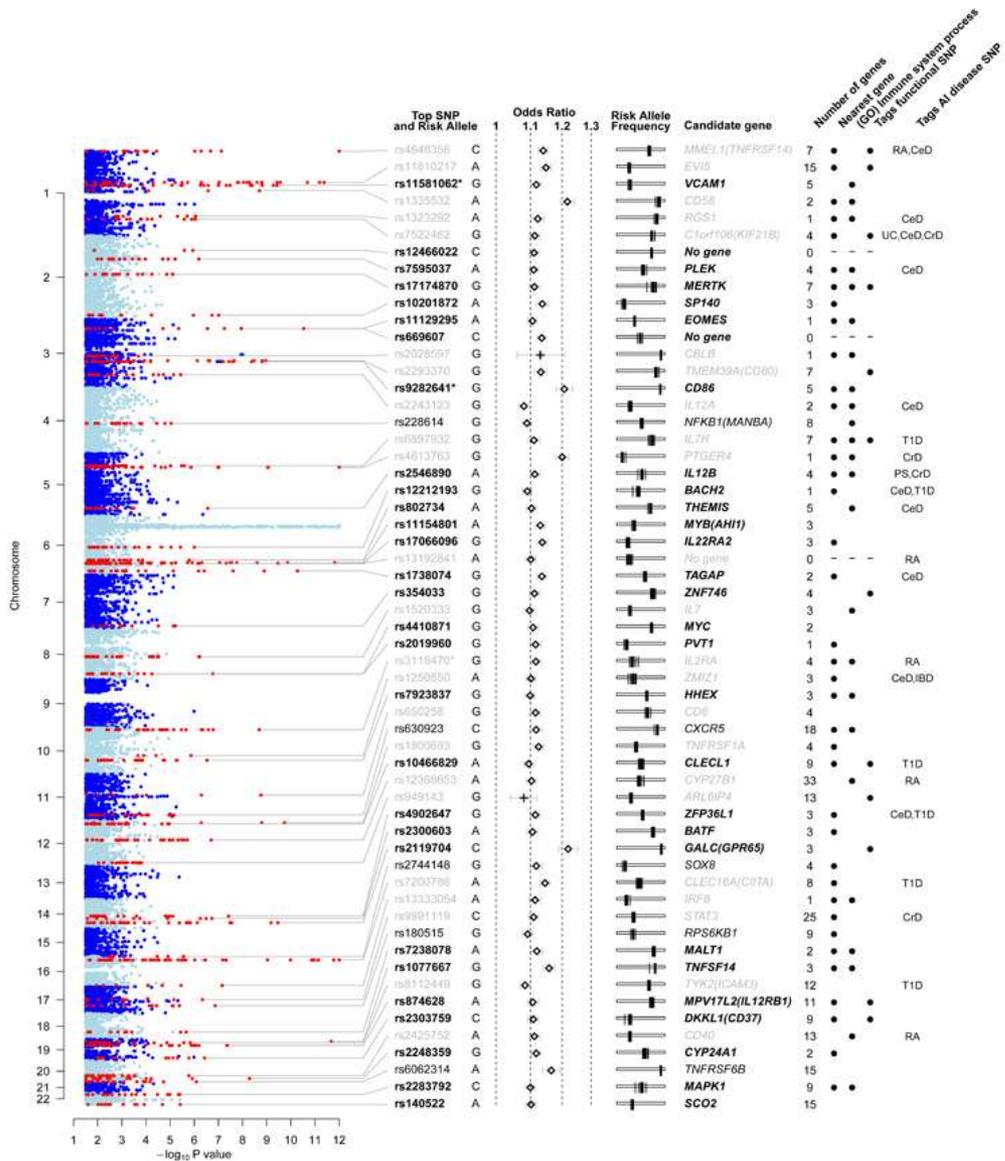
S Sawcer *et al. Nature* **476**, 214-219 (2011) doi:10.1038/nature10251

Results for the main MHC alleles.



S Sawcer *et al. Nature* **476**, 214-219 (2011) doi:10.1038/nature10251

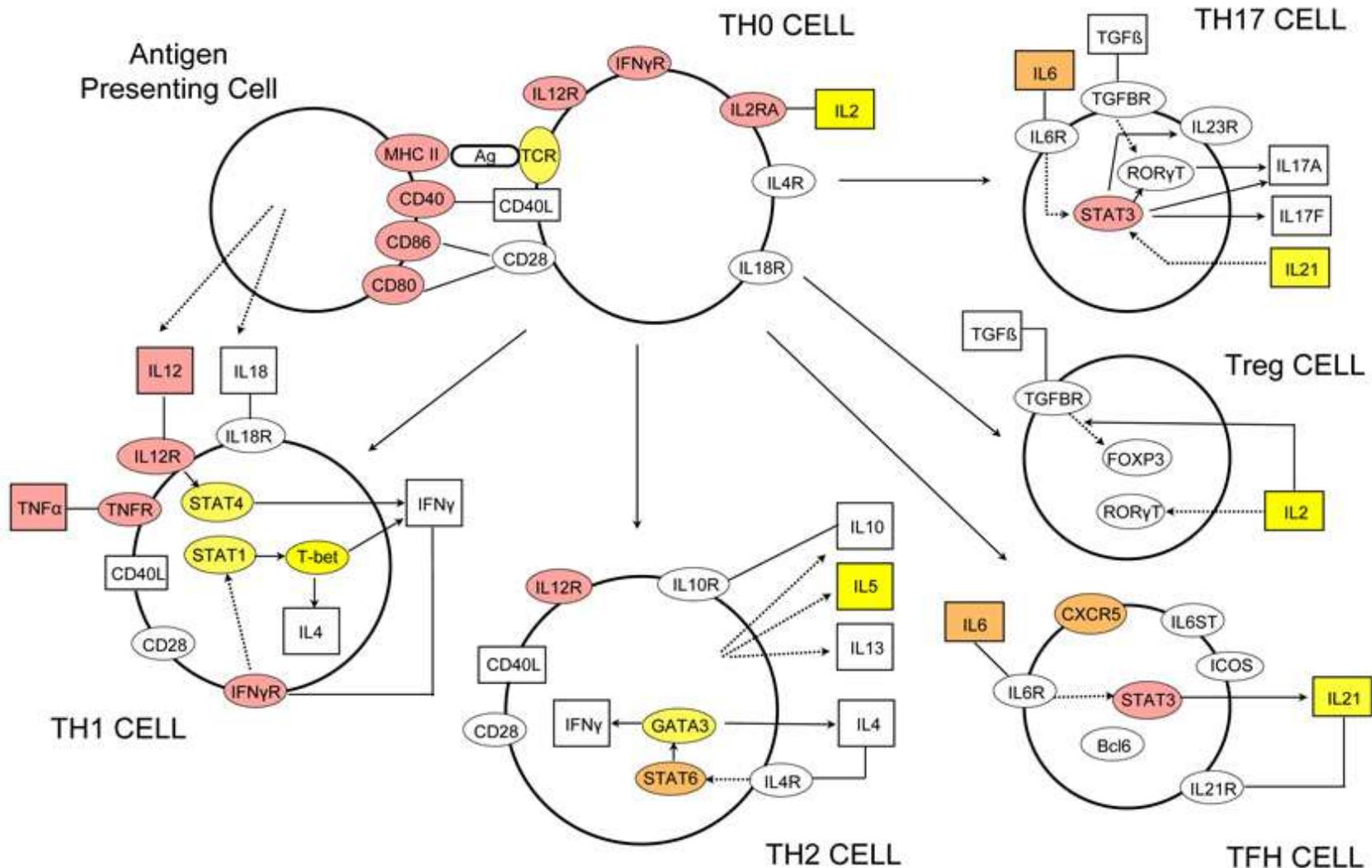
Regions of the genome showing association to multiple sclerosis



Non-MHC regions containing associated SNPs are shown in red

Black dots indicate that the candidate gene is physically included in the “immune system process” GO term.

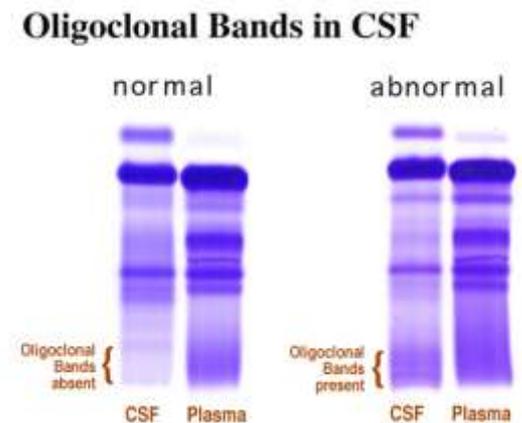
Graphical representation of the T helper cell differentiation pathway and MS susceptibility



Coloured nodes are those containing a gene implicated by proximity to a SNP showing evidence of association. The International Multiple Sclerosis Genetics Consortium (IMSGC), **Nature 2011**

3. CSF immunological abnormalities

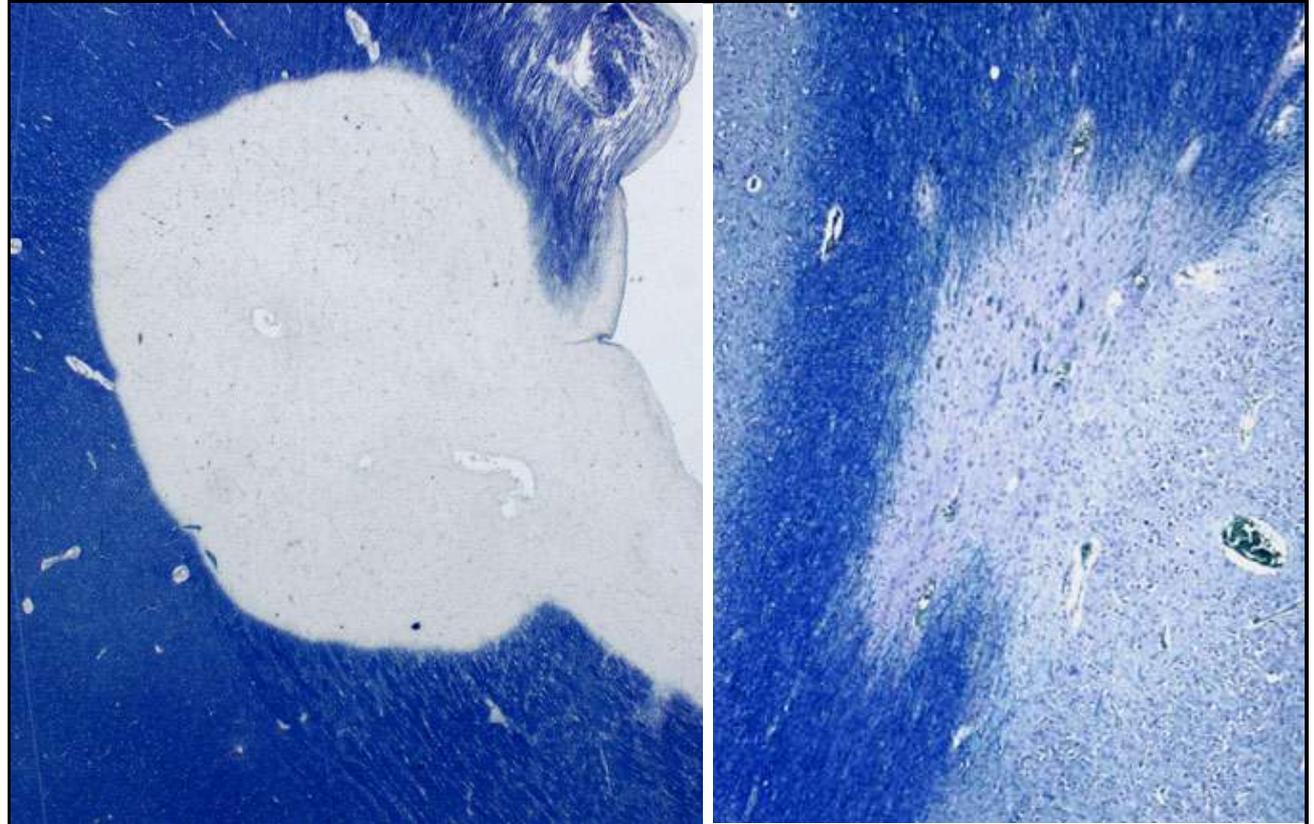
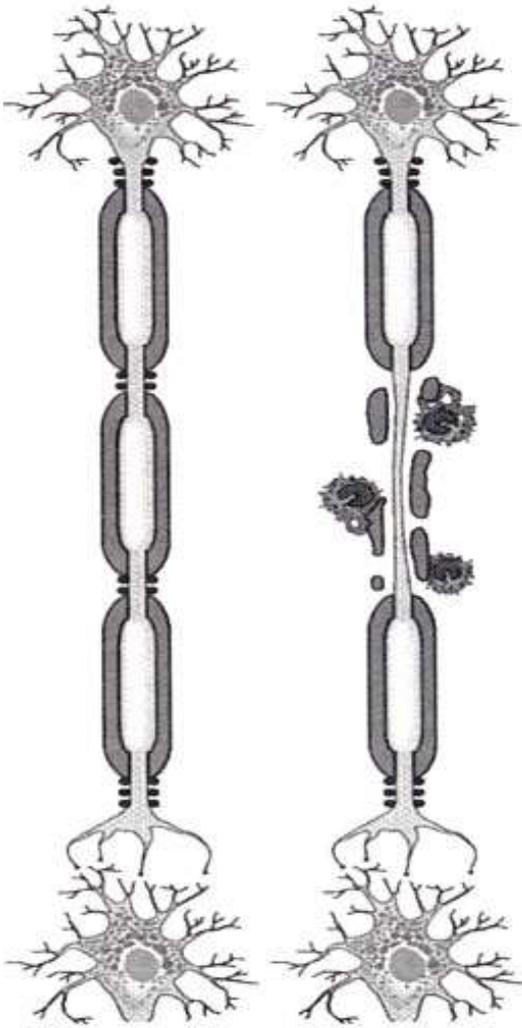
- Leukocyte counts counts can be normal but are often mildly increased above the normal of ≈ 3000 leukocytes/mL
- In MS 80% of total CSF cells are T cells (45% in blood), mainly memory T cells (up to 30% of CSF cells during inflammation), 5% are monocytes, $\leq 1\%$ B cells, plasma cells
- There can be a minor protein increase
- Increased production of IgG in the CNS
- CSF oligoclonal bands are very frequent detected in MS and stable over years



4. Subtle alteration of blood T cell functions

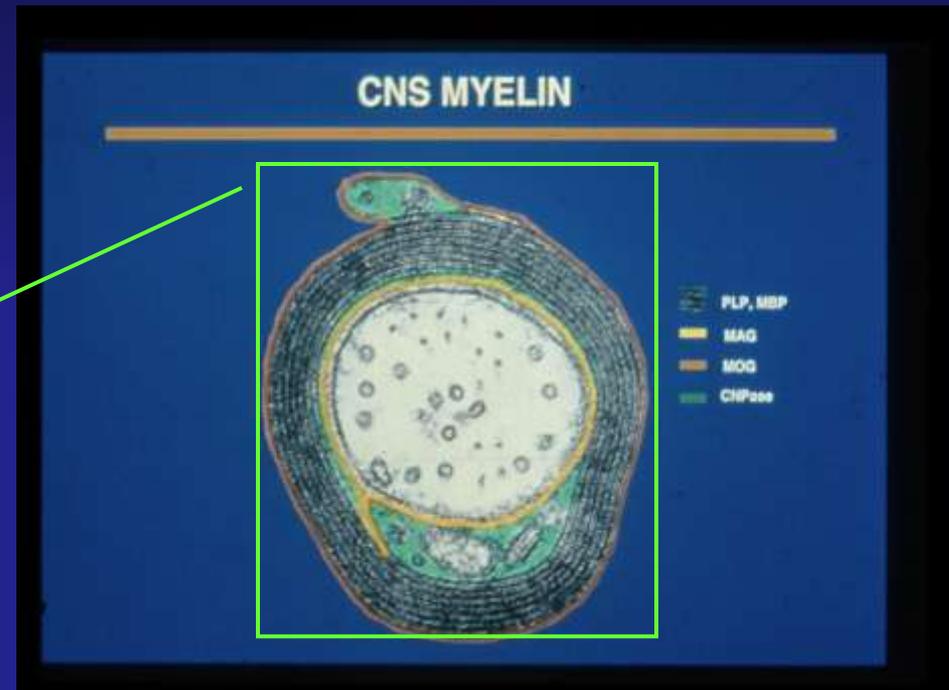
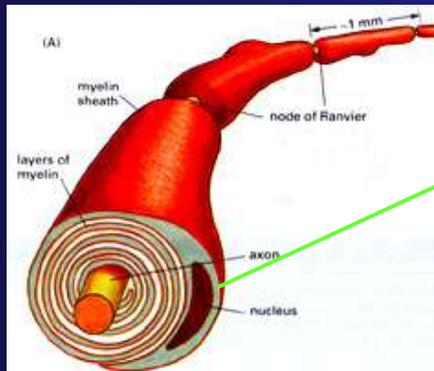
- Slightly increased frequency and reduced requirements for activation of T cells responding to myelin antigens
- Reduced activity of (CD4+/CD25+) regulatory T cells
- Prevalence of T helper 1 over T helper 2 cytokine secretion by *myelin* antigen-specific T cells

Demyelination in MS



The borders of chronic silent lesions are usually well defined whereas the borders of active lesions are more ragged

Candidate target myelin antigens in MS



Myelin basic protein (MBP); 170 aa, several isoforms)

Proteolipid protein (PLP); 272 aa, two isoforms)

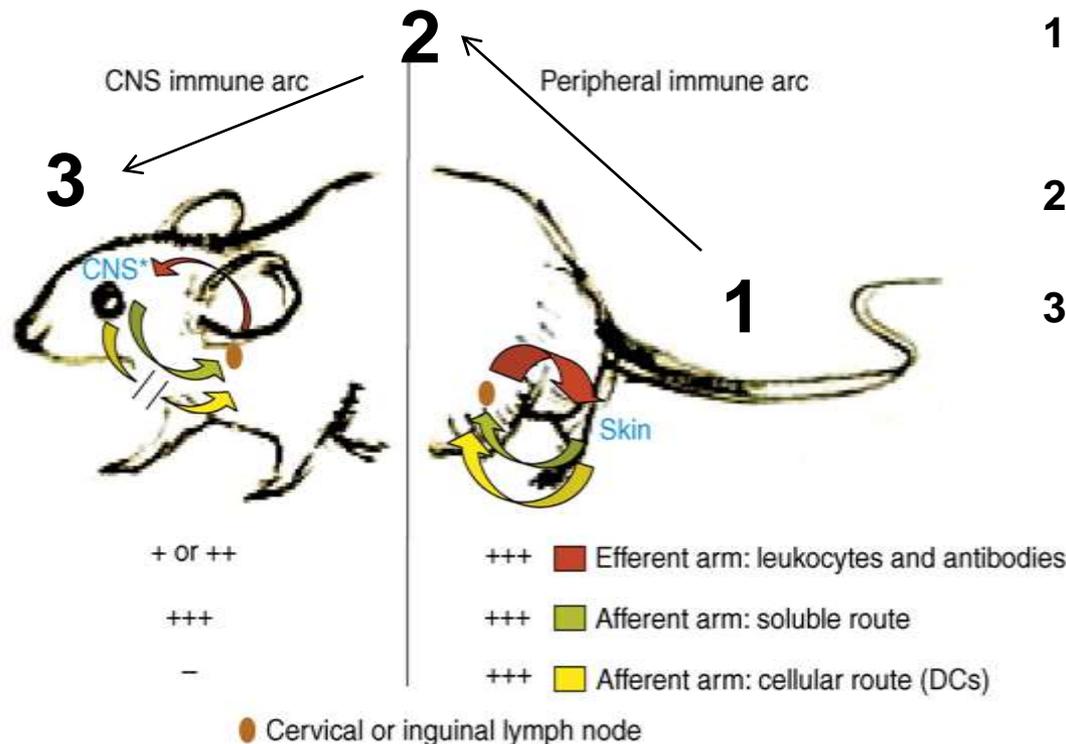
Myelin oligodendroglia glycoprotein (MOG); target of T- and B cell response)

A few others

5. Animal models of autoimmune disease

Experimental allergic encephalomyelitis (EAE):

- Induced by peripheral immunisation with myelin protein antigens
- Mediated by CD4+ myelin-specific T cells



6. Comorbidity and similarities with other autoimmune diseases

Patients with MS have increased incidence of some autoimmune conditions (best evidence is for thyroiditis) and asymptomatic positivity for autoantibodies

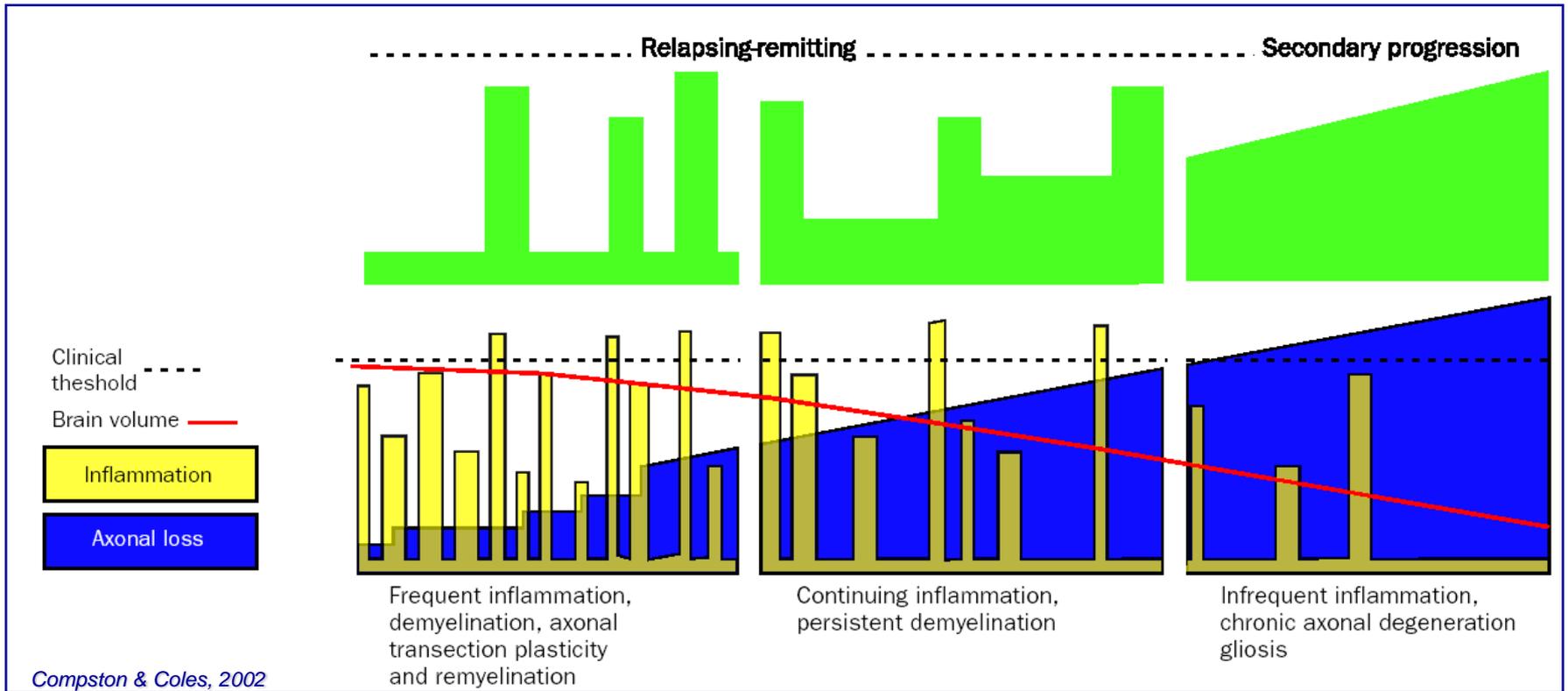
MS share with Rheumatoid Arthritis, Systemic lupus Erythematosus, autoimmune thyroiditis and other autoimmune disorders features such as:

- higher incidence in females,
- young adult onset,
- initially relapsing course

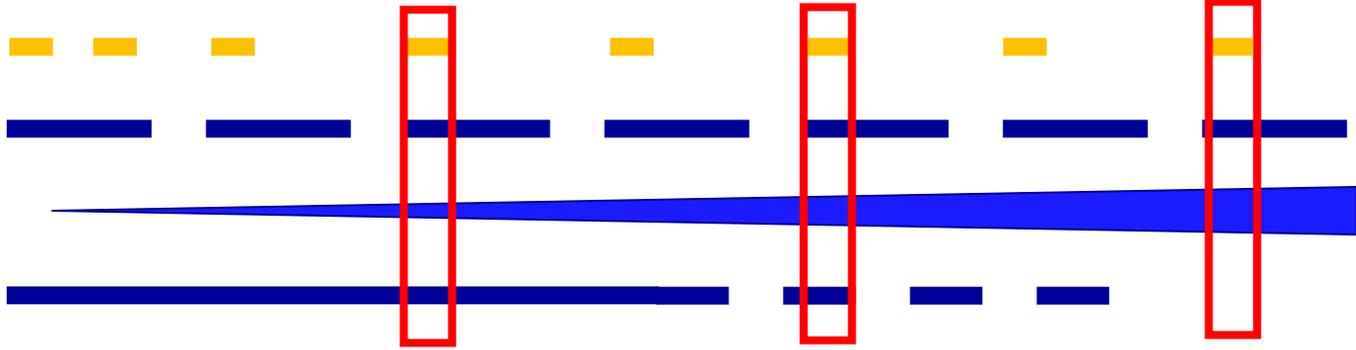
7. Response to immuno-suppressive and -modulatory therapies

MS acute relapses are improved by high-dose corticosteroid administration

The clinical course of MS is attenuated by immuno-modulatory treatment (e.g. interferon beta), by treatments blocking immune cell entry to the CNS (anti-alpha-4 integrin blockade: natalizumab) and by immuno-suppressive and cytotoxic agents (e.g. Mitoxantrone)



INFLAMMATION

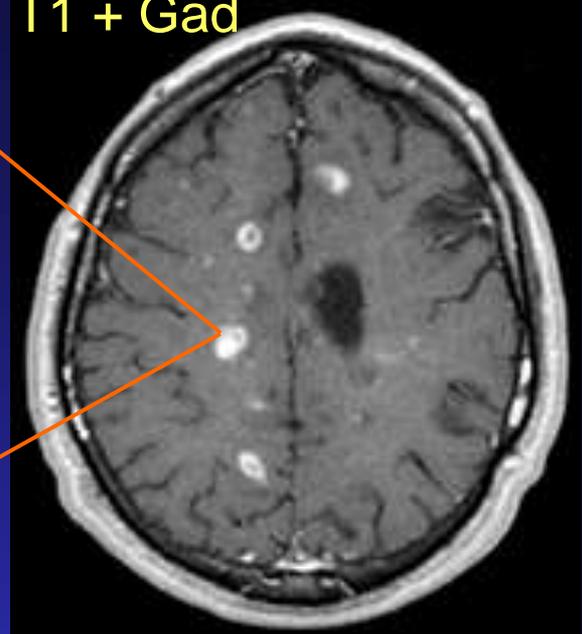


Inflammation and demyelination

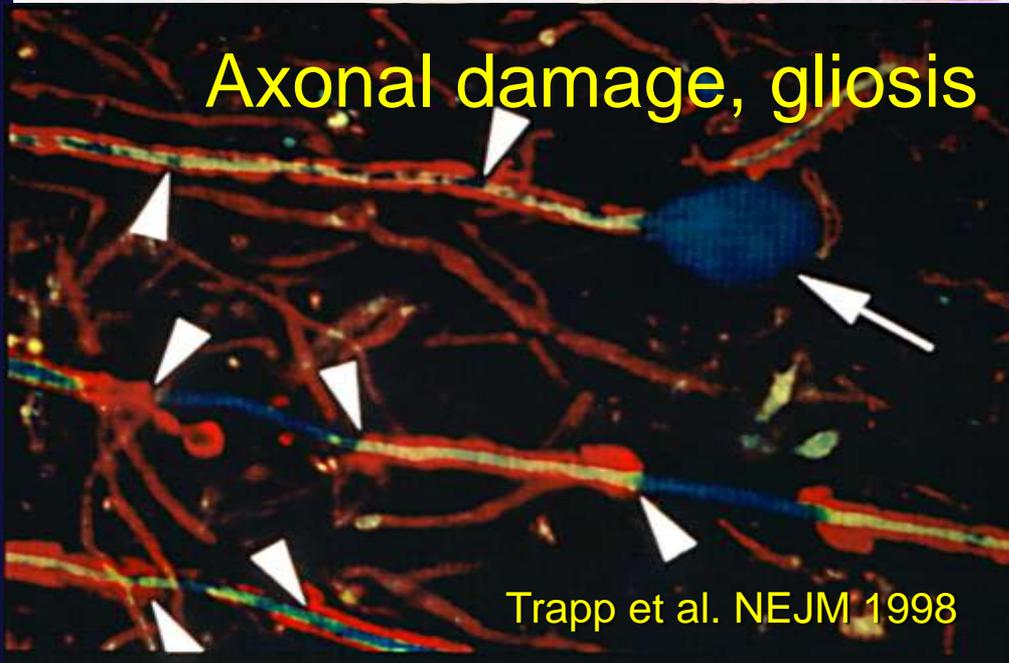


MRI

T1 + Gad

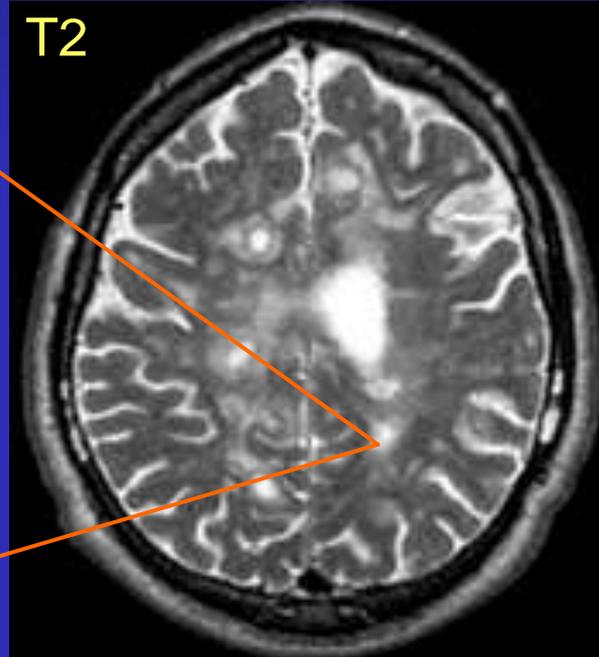


Axonal damage, gliosis



Trapp et al. NEJM 1998

T2



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Take home points

- MS is an inflammatory, likely autoimmune demyelinating and axonal disorder of the CNS
- Initiated by CD4 and/or CD8 T cells infiltrating the CNS, propagated by T cells, B cells, and plasma cells, with macrophages as common effector arm and a possible role of microglia
- Axonal degeneration is at least initially strictly dependent on inflammation, but may progress independently later on

Recommended reading

Books:

- McAlpine's Multiple Sclerosis, Fourth Edition, Churchill Livingstone, 2005 (relevant sections)

Review and original articles:

- Compston & Coles (2008) Multiple Sclerosis. Lancet.
- Prineas et al (2001) Immunopathology of secondary progressive MS. Ann Neurol 50:646-657.
- Peterson et al (2001) Transected neurites, apoptotic neurons, and reduced inflammation in cortical MS lesions. Ann Neurol 50:389-400.
- Kutzelnigg et al (2005) Cortical demyelination and diffuse white matter injury in MS. Brain 128:2705-2712.
- Magliozzi et al (2007) Meningeal B-cell follicles in secondary progressive MS associate with early onset of disease and severe cortical pathology. Brain 130:1089-1104.
- International Multiple Sclerosis Genetics Consortium; Wellcome Trust Case Control Consortium 2. Sawcer et al. Nature. 2011 Aug 10;476(7359):214-9. doi: 10.1038/nature10251.

Questions?