Immunological processes in Multiple Sclerosis

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2014 Regional MS summit
Multiple Sclerosis

MS is a chronic, often disabling disease of the central nervous system.

MS involves an autoimmune process where the immune system sees the myelin sheath surrounding our nerves as a foreign entity and attacks it, like it would viruses and bacteria.

How widespread is MS?

• Worldwide: 2.5 million people have MS
• MS currently affects 400,000 Americans, appx. 1 in 750
• The northwest has the highest incidence of MS in the country.
Complex disease

One of the Confounding Factor in Understanding and Treating MS: Heterogeneity
Different disease course

- Relapsing-remitting
- Secondary progressive (following relapsing-remitting)
- Primary-progressive
- Progressive-relapsing
## Pattern of lesions in MS

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Immunology</th>
<th>Oligos</th>
<th>Border</th>
<th>MRI</th>
<th>Model?</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>CD8 T cells and macrophages</td>
<td>Survive, rapid remyelination</td>
<td>Sharp</td>
<td>T2 ring; T1 enhancement</td>
<td>Myelin basic protein-induced experimental autoimmune encephalomyelitis NB, experimental autoimmune encephalomyelitis is CD4 cell-mediated</td>
</tr>
<tr>
<td>18% of 201 patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>II</td>
<td>As in I, plus antibodies and complement</td>
<td>Survive, rapid remyelination</td>
<td>Sharp</td>
<td></td>
<td>Myelin oligodendrocyte glycoprotein-induced experimental autoimmune encephalomyelitis</td>
</tr>
<tr>
<td>56%</td>
<td></td>
<td>Recruited proteolipid protein plus progenitors; variable axonal density</td>
<td></td>
<td></td>
<td>Myelin-associated glycoprotein and CNP lost; myelin basic protein and proteolipid protein reduced; myelin oligodendrocyte glycoprotein normal</td>
</tr>
<tr>
<td>III</td>
<td>Activated microglia</td>
<td>Oligos destroyed; Distal oligo-opathy or dystrophy</td>
<td>Indistinct</td>
<td></td>
<td>Veins with thrombotic lesions, suggest endothelial cell damage</td>
</tr>
<tr>
<td>24%</td>
<td></td>
<td>Early loss of myelin-associated glycoprotein and CNP, Axonal damage</td>
<td>Not centered around venule</td>
<td></td>
<td>~ Virus or acute ischemia-induced white matter lesions</td>
</tr>
<tr>
<td>IV</td>
<td>Macrophages and T cells</td>
<td>Primary oligo destruction, and total loss in lesions</td>
<td>Sharp, perivenous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2%</td>
<td>Only seen in primary progressive multiple sclerosis</td>
<td>Axonal damage</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Modeling MS diversity
Experimental autoimmune encephalomyelitis (EAE)

Immunization with myelin antigens (MOG$_{35-55}$)

Priming and expansion of antigen specific CD4+ T cells

Inflammation and demyelination in the CNS resulting in paralysis
Examples of spontaneous models of EAE

2D2 (TCR\textsuperscript{MOG})

60% develop isolated optic neuritis and 4% develop spontaneous EAE

2D2 TH (BCR\textsuperscript{MOG}TCR\textsuperscript{MOG})

60% develop spontaneous disease: EAE/NMO

New strain

50-70% develop spontaneous EAE starting at 5 weeks of age

Th17 > Th1
Modeling MS diversity
Spontaneous models of EAE

- To define pre-clinical signatures of disease development

- To study important mechanisms of disease regulation

- To identify and test new targets for therapy
Immune cells and MS
T cell differentiation

- Naive
  - Th2
  - Th1
  - Th17
  - Treg

Host defense
- (IC pathogens)
- (EC pathogens)

Autoimmunity
- Allergy, asthma
- Autoimmunity
- Autoimmunity

Immunoregulation
- Tumor growth

Host defense (parasites)
Regulatory T cells

Treg arise via "altered negative selection" by self-peptides
Treg characteristics

5-10% of CD4+

Adapted: Wing et al Scand J Immunol 2005
Treg Prevent Organ-specific Autoimmune Diseases

New born mice

- d7Tx → No disease
- d3Tx → Autoimmunity (thyroiditis, gastritis, insulitis, sialoadenitis, adrenalitis, oophoritis, glomerulonephritis, polyarthritis)

Mice with deletion of Foxp3

- d7Tx → No disease

Individuals with mutations in Foxp3

- IPEX (immunodysregulation polyendocrinopathy enteropathy X-linked syndrome): Early onset enteropathy (watery diarrhea/villus atrophy), Early onset Type I DM, Thyroiditis, Eczema.
Myelin specific T cells enter the CNS during EAE

Impaired Function of Treg in MS

Viglietta V, Baecher-Allan C, Weiner HL, Hafler DA.

Induction of iTreg

Bettelli et al.,
IL-6 inhibits TGF-b-induced Foxp3 expression

Bettelli et al.,
Reciprocal induction of Th17 and iTreg is controlled by IL-6

Role of IL-6 in CNS autoimmunity

Relevance of the reciprocal induction of Th17 and iTreg in vivo

Bettelli et al.,
IL-6 and effector T cell resistance

Sci Transl Med. 2013 Jan 30;5(170):
Schneider A, Long SA, Cerosaletti K, Ni CT, Samuels P, Kita M, Buckner JH.
T cell subsets

Naïve T cells

Th1

+ IFN-γ
+ IL-6
+ TGF-β

Th2

Th17

T-reg

STAT6
GATA3
\( c-maf \)

STAT4
T-bet

ROR\( γt \)
STAT3

Foxp3

TGF-β

IL-4, IL-5, IL-13

IL-12

IFN-γ

IL-17 A, IL-17F, IL-22, IL-9, IL-21

Host defense (parasites), Allergy, asthma

Host defense (IC pathogens) Autoimmunity

Host defense (EC pathogens) Autoimmunity

Immuno-suppression
IL-6 in the balance between T-eff and T-reg

- Th17 differentiation
- Effector T cell resistance

T-eff

T-reg

Treg inhibition

Th17

Th1
Pathogenic cells in EAE and MS (1)

Cua et al. 2003 (Nature, 421:744)

Pathogenic cells in EAE and MS (2)

Th17 and Th1 cells infiltrate the CNS of mice with EAE and myelin specific and Th17 and Th1 cells can transfer EAE in mice

**TH17 CELLS: HIGHLY PATHOGENIC**

Th17 cell frequency increase in the blood and CSF of MS patients during relapses
Th17 in MS

September 2009
Th17 in MS (2)


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What is difference between Th1 and Th17-induced disease?

Th17 induce the formation of CNS lymphoid follicles

Peters et al., Immunity 35, 986–996, December 23, 2011
The formation of lymphoid follicles is partially dependent on IL-17

Peters et al., Immunity 35, 986–996, December 23, 2011
Localization of lesions: Th1 vs. Th17 cells

Adapted from Goverman. Nature Reviews Immunology 9, 393-407 (June 2009)
Th17-induced pathology
IL-23 vs. IL-17 in EAE (1)

Clear role for IL-23 in disease (EAE) development (IL-23R KO, IL-23p19)


Th17-induced pathology: IL-23 vs. IL-17 in EAE (2)

However, the requirement for Th17 cells in the induction of autoimmune disorders has been questioned based on the following observations:

IL-17A knockout (KO) mice are only partially resistant to the development of EAE (Komiyama et al., 2006; Yang et al., 2008a).

Th17 cells are very unstable, loose IL-17 expression and became Th1 cells in vitro and in vivo (Bending et al., 2009; Lee et al., 2009).

Th17 cells require T-bet to induce EAE (Yang et al., 2009).
**Th cell plasticity**

Modified from: O’Shea and Paul, Science, 2010
Th17 plasticity in EAE

IL-17+ IFN-g+ T cells are present in target tissues in many autoimmune diseases.
IL-17+IFN-γ+ T cells are enriched in MOG-specific, pathogenic effector T cells
IL-23 favors the development of IL-17+IFN-γ+ cells

WT or KO mice

TGF-β + IL-6 → Th17

Naive CD4+

+IL-23 for two more rounds of stimulation

Duhen et al., Cutting Edge J Immunol. 2013 May 1;190(9):4478-82.
IL-17+ IFN-g+ T cells are generated and induce disease independently of T-bet.

Duhen et al., Cutting Edge J Immunol. 2013 May 1;190(9):4478-82.
IL-17 A cell fate mapping mouse shows that most IFN-g+ Th cells infiltrating the CNS are ex-Th17

Therapies

- Bone Marrow Transplantation
- Alemtuzumab
- Natalizumab (JC Virus+)
- Natalizumab (JC Virus-)
- Ocrelizumab
- Rituximab
- Daclizumab
- Cyclophosphamide
- Fingolimod
- Dimethyl Fumarate
- Mitoxantrone
- Azathioprime
- Teriflunomide
- Glatiramer Acetate Interferons

Labels:
- E: Emerging
- O: Off-Label
- O: Oral
- P: Parenteral
Understanding the mechanism of action of current therapies is critical.
Anti-Itga4 antibody
Understanding Itga4b1 biology and its selective effect on T cells


Lymph nodes (gated on CD4 T cells)

Naive

After Immunization

Integrin $\alpha_4$

Role of T cell specific deletion of Itga4 on EAE development

Itga4 deletion in T cells limits Th1 but not Th17 trafficking in the CNS.

Treg control disease progression

Figure: Clinical analysis of CD4\textsuperscript{Cre} Itga\textsubscript{4}\textsuperscript{fl/fl} mice immunized with MOG\textsubscript{35-55} in CFA. Anti-CD25 (PC61) or isotype control was administered at day 0. Clinical score was monitored over 30 days after immunization. Tregs control disease susceptibility in CD4\textsuperscript{Cre} Itga\textsubscript{4}\textsuperscript{fl/fl} mice.
Is the entry of Treg in CNS dependent on Itga4?

**Diagram:**
- **Tregs** and **Teff**
- **CD4** axis
- **Itga4** axis

**Graphs:**
- **Foxp3**
  - WT
  - Itga4\(^{fl/fl}\) Foxp3\(^{Cre}\)
- **Abs number CD4 + Foxp3\(^{+}\) cells**
  - WT
  - Foxp3\(^{Cre}\) Itga4\(^{fl/fl}\)
Lymphocytes express S1PR1 and exit lymphoid organs in response to S1P

- S1PR1 is required for T cell egress from thymus and for T and B cell egress from spleen, lymph nodes, tonsil
- Activated lymphocytes transiently down-regulate S1PR1 and are retained in the responding lymphoid tissue until they become effectors
- FTY720 (Fingolimod) inhibits egress and is in clinical development as an immunosuppressant (FDA approved in 2010 for treatment of multiple sclerosis)
Undergoing studies: Modulation of Treg functions upon inhibition of S1P-S1P1 axis

Analyze Treg from MS patients treated with fingolimod.
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