Immunology of Multiple Sclerosis: from bench to bedside

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The Rocky Mountain MS Center
At the University of Colorado

Disclosures

- Research grants from Biogen, Rocky Mountain MS Center, Novartis, Acorda

- Consulting for Genzyme, Genentech, Teva, Novartis, and Biogen
Objectives

• MS as an autoimmune disease

• Introduction of the immune system
  • Types of immunity
  • The players

• How do MS drugs affect the immune system

MS Pathology

Overview of the immune system

Immune system

Innate/Natural Immunity (non-specific responses)
- 1st line
  - active antibacterial enzymes
  - tissue antibacterial enzymes
  - stomach acid
- 2nd line
  - nasal passages
  - nasal linings

Adaptive/Acquired Immunity (specific responses)
- 3rd line
  - 1. Innate immune cells
  - 2. Inflammation
  - 3. Complement
  - 4. Antimicrobial substances

Specialized Lymphocytes
- B cells (produce antibodies)
- T cells
  - Helper T cells
  - Killer T cells

Innate vs Adaptive Immunity – They talk to each other

INNATE ('NATURAL')
- Interferon
- Lysis (bacteria)
- Complement
- Acute inflammation
- Tissue damage

ADAPTIVE
- entry block neutralization (Coxin)
- antibody
- Specific antigen, (all bacteria, viruses, etc.)
- T lymphocytes
- NK cells
- Cytotoxicity

Tissues
Myeloid Cells
Lymphocytes
Interferons

- **Alpha**: Produced by virus infected leukocytes
  - Used to treat Hep B and C
- **Beta**: Produced by virus infected fibroblasts.
  - Used to treat MS
- **Gamma**: Produced by activated T and NK cells
  - Make MS worse
- **Lambda**: New

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The Players

Venkat, CLL topics Updates website
Ransohoff and Cardona, Nature 486, 253-262
The Lymphocyte Lineage

MS as a T cell mediated disease

http://www.msdiscovery.org/research-resources/animal-models/584-animal-arsenal-overview-animal-models-mimic-key-aspects-ms
TH1 vs TH2

Teriflunomide inhibits lymphocyte activation

Yong VW. Neurology 2002; 59: 802-809
Adaptive Immunity

Glatiramer vs Interferon Beta
Immunogenetics of MS

• Genome-wide analysis of SNPs (GWAS) studies in \(\approx 1000\) subjects identified alleles of HLA-DRA region on chromosome 6, IL-2RA gene, and IL-7RA gene associated with MS susceptibility risk.

IL = interleukin; RA = receptor \(\alpha\); SNP = single-nucleotide polymorphism.
Immunogenetics of MS

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MS as a T cell mediated disease

Table 2. Change in EDSS and MRI over 1-year follow-up

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<th>Pt</th>
<th>Before treatment</th>
<th>Day 10</th>
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* EDSS at 1-year follow-up — EDSS pretreatment.
† Premature termination.


The Lymphocyte Lineage

CD52 – Alemtuzumab.
+ monocytes, dendritic cells
CD20 – Rituximab, Ocrelizumab, Ofatumumab, Ublituximab

http://selfhacked.com/2014/08/19/primer-immune-system-works-videosimages/
Cell Death from monoclonal Antibodies

Evidence supporting a role for B cells

- Antibodies and complement in active MS plaques.
- Clonally expanded plasma cells intrathecally
- Ectopic lymphoid follicles with B cells and B-cell related chemokines.
Cortical Lesions

Myelin Basic Protein

B cells and MS

Antigen presentation\textsuperscript{1,2}

CD20\textsuperscript{+} B CELL

Autoantibody production\textsuperscript{3}

Ectopic lymphoid follicle-like aggregates\textsuperscript{5,6}

Inside out Hypothesis

- Multiple pathways of the immune system are affected in MS
- Multiple sclerosis disease modifying therapies affect the immune system in many ways.

Conclusions

Hopefully, it this not sound like this...
Thank You!!
Any questions???

Did anybody call for a dogtor?