Dysregulation of B cells in Clinically Isolated Syndrome and Multiple Sclerosis

Nancy Monson, Ph.D.
Associate Professor of Neurology and Neurotherapeutics
Associate Professor of Immunology
University of Texas Southwestern Medical Center
Dallas Texas
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MedImmune, Inc.; grant support
Autoantibodies

Complement

Plasma cell

B cell

Neuron

Oligodendrocyte

APC (microglia, astrocyte)

T-CELL REACTIVATION

AXONAL DAMAGE

Autoantibodies

Complement

T cell

B cell

Plasma cell
Objectives:

- What are some important features of TM from an Immunologist’s perspective?
- Do TM patients have a different immune profile compared to ON patients?
- Can we use this information to identify patients that will develop MS?
- Do antibodies from B cells in the CSF bind to the brain?
TRANSVERSE MYELITIS

- Symptoms involve weakening of limbs or sensations of numbness due to demyelination occurring across short segments of the spinal cord.

- The presence of lesions in the brain of TM patients also increases the risk of conversion to MS.

- TM patients with brain lesions typically have a faster occurrence of a second attack than patients with optic neuritis (ON).

- ON patients have better long-term prognosis than other presentations including TM.

These differences in progression to clinically definite MS and location of initial lesions between ON and TM patients may suggest different underlying biology.
WHAT ARE THE JOBS OF A B CELL?

B cell

Activate T cells that are involved in disease

Plasma Cell

Produce antibodies that are involved in the disease

Cytokines
3 QUESTIONS WE ARE ASKING:

1. Are there highly activated B cells in the blood of TM patients?

2. Can we use antibody genetics to determine which TM patients will convert to MS?

3. Do antibodies from TM patients bind to the brain?
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B cell → Plasma Cell

CEREBROSPINAL FLUID

BLOOD

CD19

CD27

CD27

CSF TM

ON CD27^{LO} TM CD27^{HI} TM CD27^{LO}

ON CD27^{LO} TM CD27^{HI} TM CD27^{LO}
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B cell antibody genetics can be used to classify important disease groups

Antibody Gene Signature Score (AGS)

Has MS or CIS that convert to MS

N=21
B cell antibody genetics can be used to classify important disease groups


Over 100,000 codons analyzed

Antibody Gene Signature Score (AGS)

Has MS or CIS that convert to MS

Does not have MS

N=21

N=5

B cell antibody genetics can be used to classify important disease groups.

- Antibody Gene Signature Score (AGS)
  - Over 100,000 codons analyzed
  - N=21
  - N=5

- Has MS or CIS that convert to MS
  - P<10^{-5}
  - 93% PPV
  - 100% NPV
  - 94% Accuracy

- Does not have MS

Cameron et al. (2009) *Journal of Neuroimmunology*: 213, 123-130 and unpublished data

MSPrecise/DioGenix
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3. Do antibodies from TM patients bind to the brain?
Test for binding to brain tissue

Collect antibody from the culture media
Monoclonal antibodies made by B cells in the CSF of MS patients and patients at high risk to develop MS bind to neurons and astrocytes.
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Monoclonal antibodies made by B cells in the CSF of MS patients and patients at high risk to develop MS bind to neurons and astrocytes.

**Patient 1:**
- **CDMS**
  - AJL02: neurons
  - AJL02: astrocytes

**Patient 2:**
- **CIS-ON**
  - AJL10: neurons

**Patient 2:**
- **CIS-ON**
  - WR13: astrocytes
Monoclonal antibodies made by B cells in the CSF of MS patients and patients at high risk to develop MS bind to neurons and astrocytes.

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Monson Lab
Ann Ligocki
William Rounds
Sara Ireland
Ding Chen
Jackie Rivas
PJ Henson

Repository Team
Ben Greenberg
Paula Hardeman
Parul Chaudhary
Sam Hughes
James Alewine

Antibody Genetics Collaborators
Elliot Frohman
Sally Ward
Ann Stowe
Min Li

Antibody Genetics Support
Richard Scheuermann
Lindsay Cowell
Andy Fire
Scott Boyd

Basic Neurochemistry, 6th ed., GJ Siegel et al, photo by C. Raine