Immune Dysregulation in Secondary Progressive MS

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Learning Objectives

- Learn about the dual roles of inflammation and neurodegeneration in MS
- Learn about the different stages of MS
- Discuss potential immune biomarkers in SPMS
Natural History of MS
The Autoimmune Theory of Multiple Sclerosis

• There is abnormal neuroinflammation but no consistent evidence for infectious agent in MS lesions

• The genes associated with susceptibility to MS are immune related

• Similarities between multiple sclerosis and ADEM/ EAE
Demyelination and Inflammation in the Spinal Cord

EAE

CONTROL

MBP
DAPI
The Two Aspects of Pathology in MS: Inflammation and Neurodegeneration
Axonal Pathology in the Optic Nerve during EAE
Demyelination and Axonopathy in the VCO of a mouse with conventional EAE

SMI32
MBP
DAPI
Is autoimmune inflammation still relevant during the SP stage of MS?

Evidence against a role of inflammation in SPMS

- Gadolinium enhancing activity (caused by new foci of inflammation) diminishes over time and does not correlate with progressive disability

- DMT that suppress or modulate the peripheral immune system are less effective in SPMS than RRMS

Evidence supporting a role of inflammation in SPMS

- Peripheral immune abnormalities are more prominent in patients with SPMS

- Aggressive chemotherapy (ex. Mitoxantrone) stabilizes some patients with SPMS

- Lymphoid follicles have been detected in the meninges of brain tissues from individuals with SPMS (Shift of autoimmune “headquarters” from peripheral lymphoid tissues to CNS?)
A 12 month longitudinal study of myelin-specific cytokine responses and MRI lesion development in RR and SP MS

- **Patient Population**
  
  12 RRMS  
  26 SPMS  
  39 Healthy Controls

- **Protocol**
  
  Phlebotomy - every 4 weeks  
  MRI (contrast enhanced) - every 8 weeks  
  EDSS evaluation every - every 12 weeks

- **Immunological Assay**
  
  IFN\(_\gamma\) and IL-17 Elispots - performed directly \textit{ex vivo}  
  - Stimuli: whole human MBP  
    Tetanus Toxoid  
  
  Luminex assays
MBP-specific Th1 and Th17 PBMC are more frequent in RRMS and SPMS than HC.

Th1 personal average
- RR vs HC p < .01
- SP vs HC p < .01
- SP vs RR p = 0.792

Th1 personal variance
- RR vs HC p < .01
- SP vs HC p < .01
- SP vs RR p = 0.722

Th17 personal average
- RR vs HC p < .01
- SP vs HC p < .01
- SP vs RR p = 0.114

Th17 personal variance
- RR vs HC p < .01
- SP vs HC p < .01
- SP vs RR p = 0.016
The frequencies of TT-specific Th1 and Th17 PBMC are comparable in MS and HC.
The frequency of MBP-specific Th17 PBMC is stable over time
The Th17 response increases with disease duration.
Plasma levels of IL-17 inducible chemokines correlate with disease duration.

- **CCL2**: $R=0.459$, $p<0.001$
- **CXCL1**: $R=0.208$, $p=0.006$
- **CCL11**: $R=0.345$, $p<0.001$
- **Neutrophil elastase**: $R=0.452$, $p<0.001$
Expression of Th17 cells and myeloid chemokines correlates with EDSS

MBP-reactive Th17 cells

R=0.270
p<0.001

R=0.351
p<0.001

R=0.320
p<0.001

R=0.305
p<0.001

Expression of Th17 cells and myeloid chemokines correlates with EDSS.
Plasma levels of IL-17 inducible chemokines are upregulated in SPMS vs RRMS
Plasma levels of IL-17 inducible chemokines correlate with MRI T1 lesion load

CCL2

G-CSF

CCL11

Normalized T1 lesion volume

Normalized T1 lesion volume

Normalized T1 lesion volume

R=.502

R=.352

R=.448

p<0.001

p<0.001

p<0.001
Plasma levels of IL-17 inducible factors correlate with MRI T2 lesion load

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<th>Immune parameter</th>
<th>Correlation (R)</th>
<th>Significance (p value)</th>
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<td>CCL2</td>
<td>.339</td>
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<td>CXCL1</td>
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<td>Neutrophil Elastase</td>
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<td>G-CSF</td>
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Plasma levels of Th17 related factors are inversely related to brain parenchymal fraction

<table>
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<th>Correlation (R)</th>
<th>Significance (p value)</th>
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<tr>
<td>IL-17</td>
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<td>IL-23</td>
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<td>Neutrophil Elastase</td>
<td>-.277</td>
<td>.028</td>
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Eotaxin 3 is elevated in the CSF of SPMS patients

- Eotaxin 3 pg/ml

- Ctrl
- RRMS
- SPMS

- p = 0.0085
- p < 0.0001
- p < 0.0001

- Ctrl
- RRMS
- SPMS
Conclusions

• MBP-specific Th1 and Th17 cells are enriched in the peripheral T cell repertoire of individuals with MS (?epiphenomenon or causal relationship)?

• Immune dysregulation persists in individuals with SPMS

• IL-17 and related cytokines are potential therapeutic targets for the treatment of SPMS.
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