Multiple Sclerosis: 30 Years of Progress

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Disclosures

• Dr. Bourdette has research grants from the Department of Veterans Affairs, the National Institutes of Health and National MS Society

• Dr. Bourdette has received education grants and honoraria for speaking from Teva Neurosciences, BiogenIdec, and Serono EMD
Learning Objectives

At the conclusion of this activity, the participant will be able to:

• A. Describe that MS is both an inflammatory and neurodegeneration disease that involves myelin, axons and neurons.

• B. Describe what is currently known about the genetic and environmental influences on the risk of developing MS.

• C. Understand that there are disease modifying therapies for relapsing remitting MS but that we need to develop therapies for progressive MS.
Obtaining CME Credit

• If you would like to receive CME credit for this activity, please visit:

   http://www.pesgce.com/PVAsummit2011/

• This information can also be found in the Summit 2011 Program on page 8.
Saint Lidwina of Schiedam
(1380-1433)
Jean-Martin Charcot (1825-1883)
The Big Questions

• What is MS?
• What causes MS?
• How do we treat and ultimately cure MS?
Multiple Sclerosis 1981

- MS was an inflammatory, autoimmune demyelinating disease of the CNS.
- MS required genetic predisposition and some unknown environmental exposure.
  - HLA-DR2
- We could treat relapses with corticosteroids.
Multiple Sclerosis 1981

• MS was an inflammatory, autoimmune demyelinating disease of the CNS.

• MS required genetic predisposition and some unknown environmental exposure.
  – HLA-DR2

• We could treat relapses with corticosteroids.
Joseph Babinski (1857-1932)
Model of Acute MS Lesion
Gadolinium Enhancement on MRI Shows Inflammation in MS
Clinical Course of MS

Relapsing Remitting Disease
Secondary Progressive Disease

MRI Lesions

Time

Neurologic Impairment
MS is a Demyelinating Disease
MS and Axonal Injury

Adams, A Colour Atlas of Multiple Sclerosis, 1989
Axonal Injury in Acute MS Lesions

“Dying Back Axonopathy” in MS

Trapp and Stys, Lancet Neuro 8: 280–91, 2009
MS Involves Inflammation and Neurodegeneration

Inflammation

Neurodegeneration

RRMS  SPMS  PPMS
Multiple Sclerosis 2011

- MS is an inflammatory and neurodegenerative disease that affects myelin, axons and neurons
- Risk of MS relates to multiple genes and reduced sunlight exposure and low vitamin D levels
- Several anti-inflammatory drugs control RRMS but we do not have disease modifying therapies for progressive MS
Multiple Sclerosis 1981

- **MS** is an inflammatory, autoimmune demyelinating disease of the CNS.

- **MS** requires genetic predisposition and some unknown environmental exposure.
  - HLA-DR2

- **We can treat relapses with corticosteroids.**
Genes and MS

- HLA-DR2 remains gene with strongest influence on risk
- >50 genes have been associated with altering the risk of developing MS
Latitude Influences Risk of MS

Low sunlight
Low vitamin D
Multiple Sclerosis 2011

• MS is an inflammatory and neurodegenerative disease that affects myelin, axons and neurons

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Multiple Sclerosis 1981

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- We could treat relapses with corticosteroids.
FDA Approved Disease Modifying Therapies for MS

- Interferon beta (4 forms)
- Glatiramer acetate
- Natalizumab
- Fingolimod

- Mitoxantrone*
Summary of Current DMTs

• They all reduce frequency of relapses and new brain lesions
• They reduce risk of increased permanent impairment in RRMS
• They differ in route of administration, efficacy, and side-effect profiles
• They are all very expensive
• None have proven useful in treating progressive forms of MS
Multiple Sclerosis 2011

- MS is an inflammatory and neurodegenerative disease that affects myelin, axons and neurons
- Risk of MS relates to multiple genes and reduced sunlight exposure and low vitamin D levels
- Several anti-inflammatory drugs control RRMS but we do not have disease modifying therapies for progressive MS
Treatments for MS Need to Target Different Mechanisms

- Inflammation
- Neurodegeneration
- Immunotherapies
- Neuroprotection/Neural Repair

RRMS | SPMS | PPMS
The Mitochondrial Hypothesis

![Mitochondria Inner Structure Diagram](image)

- Inner Membrane
- Outer Membrane
- Cristae
- Matrix
- ATP
- Ca$^{2+}$
Axonal Mitochondria

Acute: Immune Cells

Microglia

Chronic: Axonopathy

ATP Collapse

Axonal Degeneration

Ca^{2+}

NO

Free Radicals

PTP Opening**

Ca^{2+}

ATP Synthesis

ETC

H^{+}

ADP + Pi

ATP

H^{+}

H^{+}

NO

Ca^{2+}

Ca^{2+}

Glutamate

T cells

iNOS

Microglia

Ca^{2+}

NO

PTP

Ca^{2+}

Overload
Gray Matter is Lost in Multiple Sclerosis

Whole Brain Tissue Volumes

<table>
<thead>
<tr>
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<th>Gray Matter</th>
<th>White Matter</th>
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<td>Volume (mm³)</td>
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<td>6e+05</td>
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<td>2e+05</td>
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Lesion Volumes

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<td>Females/Total Subjects</td>
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7T $^{31}$P MR Spectrum from Human Brain

- $\gamma$-ATP
- $\alpha$-ATP
- $\beta$-ATP
Reduced $^{31}$P Signal Levels in Multiple Sclerosis

Whole Brain Average

Grey Matter Average

White Matter Average
Axonal Mitochondria

Acute: Immune Cells

Chronic: Axonopathy

Microglia

NO

Ca\(^{2+}\)

PTP Opening**

Anti-oxidants

Free Radicals

Ca\(^{2+}\)

ATP Collapse

Axonal Degeneration

Ca\(^{2+}\) Overload
Lipoic Acid
Experimental Autoimmune Encephalomyelitis
Lipoic Acid Treats a Mouse Model of MS

Days Post Immunization
Average Clinical Score

- 69 (Control)
- 68 (Vehicle)
- 67 (2mg/mL LA)
Axonal Mitochondria

Acute:
Immune Cells

Chronic:
Axonopathy

Microglia

AtP Collapse

Axonal Degeneration

Ca^{2+}

NO

Free Radicals

CyP D

PTP Opening**

ATP Synthase

ADP + Pi → ATP

ATPase

ETC

Ca^{2+}

Ca^{2+}

Overload

NO

iNOS

Glutamate

CyP

Membrane Na^+ / Ca^{2+}

Emelination Channel
CyPD-Null Mice Develop EAE and Recover

Forte et al, PNAS, 2007
CyPD-Null Mice with EAE have Reduced Axonal Injury

Naive

WT EAE

CyPD-KO EAE
CyPD-Null Mice with EAE have Inflammation in the Spinal Cord

CD4+ T Cells

CD11b+ Monocytes /Microglia

WT EAE  CyPD-Null EAE
Debio 025 Suppresses EAE in mdr1a-Null Mice
What Causes MS?

• Genetic predisposition
  – >50 genes influence the risk of MS and nearly all are related to the immune system

• Environmental Exposure
  – Low sun exposure and low vitamin D

Virus???
Japanese Macaque Encephalomyelitis

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- Female
- Male
MRI Reveals Lesions in Brain and Cervical Cord
Pathology Reveals Inflammation, Demyelination and Axonal Injury
Japanese Macaque Rhadinovirus

- **Gamma herpes virus**
  - 90% sequence homology with rhesus rhadinovirus
  - vIL-6 and vMCP-1

- **Low sequence homologies with known human herpes viruses**
  - EBV: 22%
  - HHV-6: 27%
  - HSV-1: 26%
  - Karposi sarcoma herpes virus: 48%
Acknowledgements

- Mike Forte, PhD
- Paolo Bernardi, MD
- Bill Rooney, PhD
- Gail Marracci, PhD
- Priya Chaudhary, PhD
- Scott Wong, PhD
- Michael Axthelm, DVM, PhD
Ratiometric pericam

Excitation 415/494 nm
Emission 515 nm
Inactivation of CyPD Increases Neuronal Mitochondrial Ca\textsuperscript{2+} Retention
Inactivation of CyPD Maintains Proton Gradient in Neuronal Mitochondria

![Graph showing TMRM intensity over time for different conditions: WT, WT+CsA, and CyPD-KO. ATP+KCl is applied at 0.5 min.](image)
Cyclosporine A and its Derivatives

There are distinct binding sites for cyclophilins and calcineurin.
CyPD-Null Neurons Resist Free Radical Injury

Forte et al PNAS 2007
Debio 025 Tissue Levels in WT vs *mrd1a-Null* Mice

Brain, Liver, Lung, Cord, Blood

*mrd1a-/-*
Acute: Immune Cells

Axonal Mitochondria

Chronic: Axonopathy

Microglia

NO

Ca\(^{2+}\)

PTP Opening**

ATP Collapse

Axonal Degeneration

Ca\(^{2+}\) Overload
Pathologic Activation of Mitochondrial PTP

- Loss of ability to produce ATP
- Increase in intracellular Ca$^{2+}$
- Release of Cytochrome C
- Activation of apoptotic pathways

But...inactivation of CyPD inhibits PTP activation
Axonal Mitochondria

Acute inflammatory attack
- T cell release proinflammatory cytokines
  - TNF-α
  - IFN-γ
  - ↑ NO
  - ↑ iNOS
  - ↑ glutamate

Microglia
- ↑ Ca²⁺

Progressive/chronic demyelination
- ↑ voltage-gated Na⁺ channel expression along axon
- ↑ metabolic demand
- Reversal of axonal membrane Na⁺/Ca²⁺ transporter

Mitochondrial dysfunction
- ATP production
  - Energy deficit
- Loss of cell homeostasis
- Impaired axonal transport
- PTP opening
  - Solute influx
  - Mitochondrial membrane potential dissipation
  - Mitochondrial swelling and rupture
  - Cytochrome C release

ETC: Electron Transport Chain
ATP synthase
ADP + Pi → ATP

O₂⁻ + NO → ONOO⁻

Uniporter
Unip.: a ion channel, a molecule transporter
Cyp D
Cyt C

Acute axotomy and axonal degeneration
Robert Carswell (1793-1857)
1st Description of MS Pathology 1838
MS is a Neurodegenerative Disease

Trapp and Stys, Lancet Neuro 8: 280–91, 2009
Saint Lidwina of Schiedam
(1380-1433)
“Virtual Hypoxia” Hypothesis

Trapp and Stys, Lancet Neuro 8: 280–91, 2009
Jean-Martin Charcot (1825-1883)
mdr1a Inhibits the Entry of Some Drugs into the CNS

Osherovich L SciBX 2009 2:773
Multiple Sclerosis and MRI