The immunopathogenesis of multiple sclerosis

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Disclosures

• Dr. Stüve has received research funding from Teva Pharmaceuticals
• Dr. Stüve is on the editorial boards of Clinical and Experimental Immunology, JAMA Neurology, Multiple Sclerosis, and Therapeutic Advances in Neurological Disorders
Learning objectives

A. To understand the role of the adaptive immune system in the initiation of relapsing-remitting MS

B. To learn about factors that cause relapses in relapsing-remitting MS

C. To comprehend events that lead to remission in relapsing-remitting MS
Multiple Sclerosis

• Inflammatory, demyelinating, neurodegenerative disease of the central nervous system
• Unknown etiology
• Presumed autoimmune pathogenesis
Multiple Sclerosis

Multiple Sclerosis

What starts the disease?

Disability

Time

Underlying Factors of MS

Genetic predisposition

Environmental factors

Infectious agent

Abnormal immunologic response → MS
Vitamin D intake and incidence of multiple sclerosis

K.L. Munger, MSc; S.M. Zhang, MD, ScD; E. O’Reilly, MSc; M.A. Hernán, MD, DrPH; M.J. Olek, DO; W.C. Willett, MD, DrPH; and A. Ascherio, MD, DrPH

Abstract—Background: A protective effect of vitamin D on risk of multiple sclerosis (MS) has been proposed, but no prospective studies have addressed this hypothesis. Methods: Dietary vitamin D intake was examined directly in relation to risk of MS in two large cohorts of women: the Nurses’ Health Study (NHS; 92,253 women followed from 1980 to 2000) and Nurses’ Health Study II (NHS II; 95,310 women followed from 1991 to 2001). Diet was assessed at baseline and updated every 4 years thereafter. During the follow-up, 173 cases of MS with onset of symptoms after baseline were confirmed. Results: The pooled age-adjusted relative risk (RR) comparing women in the highest quintile of total vitamin D intake at baseline with those in the lowest was 0.67 (95% CI = 0.40 to 1.12; \( p \) for trend = 0.03). Intake of vitamin D from supplements was also inversely associated with risk of MS; the RR comparing women with intake of ≥400 IU/day with women with no supplemental vitamin D intake was 0.59 (95% CI = 0.38 to 0.91; \( p \) for trend = 0.006). No association was found between vitamin D from food and MS incidence. Conclusion: These results support a protective effect of vitamin D intake on risk of developing MS.

NEUROLOGY 2004;62:60–65
Epstein-Barr Virus and Multiple Sclerosis

Evidence of Association From a Prospective Study With Long-term Follow-up

Gerald N. DeLorenze, PhD; Kassandra L. Munger, MSc; Evelyn T. Lennette, PhD; Norman Orentreich, MD; Joseph H. Vogelman, DEE; Alberto Ascherio, MD, DrPH
Multiple Sclerosis

• Peak age of onset: Between 20 and 40 years of age
• Female preponderance
Underlying Factors of MS

Genetic predisposition

Environmental factors

Infectious agent

Abnormal immunologic response → MS
Complex genetic diseases

- Unknown genetic parameters and mode of inheritance
- Substantial role of non-genomic factors
# Selected familial risks for MS

<table>
<thead>
<tr>
<th>Relationship to index patient</th>
<th>Age-adjusted recurrence risk (%)</th>
<th>Times risk increased compared with general population*</th>
<th>Identity descent (%)</th>
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<tr>
<td>First degree relative</td>
<td>3.0–5.0</td>
<td>15–25</td>
<td>50</td>
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<tr>
<td>Monozygotic female twin</td>
<td>34.0</td>
<td>170</td>
<td>100</td>
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<tr>
<td>Adopted first degree relative</td>
<td>0.2</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Offspring of conjugal mating</td>
<td>30.5</td>
<td>150</td>
<td>50 with each parent</td>
</tr>
</tbody>
</table>

*Lifetime prevalence in the general population is 0.2%.

David A Dyment, George C Ebers, and A Dessa Sadovnick

THE LANCET Neurology Vol 3 February 2004
Regions of overlap between whole genome scans in multiple sclerosis

<table>
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</table>
Interleukin 7 receptor α chain (IL7R) shows allelic and functional association with multiple sclerosis

Simon G Gregory1,9, Silke Schmidt1,9, Puneet Seth2, Jorge R Oksenberg3, John Hart1, Angela Prokop1, Stacy J Caillier3, Maria Ban4, An Goris5, Lisa F Barcellos6, Robin Lincoln3, Jacob L McCauley7, Stephen J Sawcer4, D A S Compston4, Benedicte Dubois5, Stephen L Hauser3, Mariano A Garcia-Blanco2, Margaret A Pericak-Vance8 & Jonathan L Haines7, for the Multiple Sclerosis Genetics Group

The NEW ENGLAND JOURNAL of MEDICINE

Risk Alleles for Multiple Sclerosis Identified by a Genomewide Study

The International Multiple Sclerosis Genetics Consortium*
Multiple Sclerosis

What causes a relapse?

Etiology of Multiple Sclerosis

- Two particular circumstances have been associated with clinical MS exacerbations:
Etiology of Multiple Sclerosis

- Two particular circumstances have been associated with clinical MS exacerbations:
  - Postpartum period
Etiology of Multiple Sclerosis

• Two particular circumstances have been associated with clinical MS exacerbations:
  – Postpartum period
  – Febrile infections
Experimental Autoimmune Encephalomyelitis (EAE)

myelin Ag./CFA s/c

+myelin Ag.

CD4+ Th1

ADOPTIVE TRANSFER

Nitin Karandikar, UTSW.
Transgenic mice that express a myelin basic protein-specific T cell receptor develop spontaneous autoimmunity

Joan Goverman\textsuperscript{a}, Andrea Woods\textsuperscript{c}, Lisa Larson\textsuperscript{a}, Leslie P. Weiner\textsuperscript{b}, Leroy Hood\textsuperscript{a} and Dennis M. Zaller\textsuperscript{c}

\textsuperscript{a} Division of Biology California Institute of Technology, Pasadena, California 91125, USA
\textsuperscript{b} Department of Neurobiology University of Southern California School of Medicine, Los Angeles, California 90033, USA
\textsuperscript{c} Department of Molecular Immunology Merck Research Laboratories, Rahway, New Jersey 07065, USA

\textbf{Cell}

\textit{Volume 72, Issue 4, 26 February 1993, Pages 551-560}
Exacerbations of multiple sclerosis in patients treated with gamma interferon.

Panitch HS, Hirsch RL, Haley AS, Johnson KP.

In an open, randomised study, 18 patients with clinically definite, relapsing-remitting multiple sclerosis (MS) received 1 microgram, 30 micrograms, or 1000 micrograms doses of recombinant gamma interferon (IFN-gamma), given by intravenous infusion twice a week for four weeks. 7 patients had exacerbations during treatment. This exacerbation rate, compared retrospectively with the pretreatment rate and prospectively with the post-treatment rate, was significantly greater than expected. Exacerbations were not precipitated by fever or other dose-dependent side-effects. A concomitant increase in circulating monocytes bearing class II (HLA-DR) surface antigen suggested that the attacks induced during treatment were immunologically mediated. IFN-gamma is unsuitable for treatment of MS.

VLA-4

Natalizumab
Fingolimod

Believed to modulate sphingosine 1-phosphate (S1P) receptors on lymphocytes and other tissues\(^1,2\)

- S1P receptors are widely expressed, including in cardiac tissue, vascular endothelium, and pulmonary endothelium\(^2,3\)

- Prevents lymphocytes from leaving the lymph nodes and entering the bloodstream and CNS compartment\(^1,4,5\)

- The mechanism by which fingolimod exerts therapeutic effects in MS is unknown\(^1\)

Central Nervous System

Circulation

T-cell extravasation

T-cell adhesion

T-cell rolling

T-cell activation

T cell

APC

B cell

T cell

B-cell – T-cell cross-activation

Plasma cell

Memory B cell

Antibodies & Complement

Inflammation

Inflammatory mediators

MBP

PLP

Oligodendrocyte

Hypoxia, ischemia

Energy depletion

Failure of Na/K ATPase

Activation of Na+ channels

Reverse Na+ Ca2+ exchange

Ca2+ Na+
B-Cell Depletion with Rituximab in Relapsing–Remitting Multiple Sclerosis

Stephen L. Hauser, M.D., Emmanuelle Waubant, M.D., Ph.D.,
Douglas L. Arnold, M.D., Timothy Vollmer, M.D., Jack Antel, M.D.,
Robert J. Fox, M.D., Amit Bar-Or, M.D., Michael Panzara, M.D.,
Neena Sarkar, Ph.D., Sunil Agarwal, M.D., Annette Langer-Gould, M.D., Ph.D.,
and Craig H. Smith, M.D., for the HERMES Trial Group*
A

Total No. of Lesions

Weeks

P < 0.001

P = 0.78

P = 0.003

P = 0.001

B

No. of New Lesions

Weeks

P < 0.001

P = 0.76

P = 0.002

P < 0.001

Placebo

Rituximab

Hauser et al. NEJM. 2008.
VLA-4

$\alpha_4 \beta_1$

Natalizumab
Circulation

Central Nervous System

T-cell extravasation

Chemoattraction

T-cell adhesion

T-cell rolling

T-cell activation

CNS APC

T-cell reactivation

B-cell – T-cell cross-activation

Plasma cell

Memory B cell

Antibodies & Complement

Inflammatory mediators

Inflammation

Hypoxia, ischemia

Energy depletion

Activation of Na+ channels

Failure of Na/K ATPase

Reverse Na+ Ca2+ exchange

Oligodendrocyte

MBP

PLP

Ca2+ Na+

K+ Na+
Multiple sclerosis flares associated with recombinant granulocyte colony-stimulating factor

Article abstract—Four of 10 patients who were enrolled on protocols of high-dose immunosuppression with peripheral blood stem cell rescue for MS experienced neurologic worsening while receiving recombinant human granulocyte colony-stimulating factor. There was improvement when methylprednisolone was given to three of the patients, but one patient died of respiratory failure. The mechanism of the neurologic worsening is uncertain. Key words: MS—Granulocyte colony-stimulating factor—Stem cell transplantation—Immunosuppression.

NEUROLOGY 2000;54:2147–2150

H. Openshaw, MD; O. Stuve, MD; J.P. Antel, MD; R. Nash, MD; B.T. Lund, PhD; L.P. Weiner, MD; A. Kashyap, MD; P. McSweeney, MD; and S. Forman, MD

<table>
<thead>
<tr>
<th>Table 2 Neurologic worsening (flares) on rhG-CSF</th>
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<tbody>
<tr>
<td>Patient</td>
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<td>---------</td>
</tr>
<tr>
<td>1</td>
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<tr>
<td>(COHNMC)</td>
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<tr>
<td>2</td>
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<td>3</td>
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<td>(FHCRC)</td>
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<td>4</td>
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<td>(MNIH)</td>
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</table>

rhG-CSF = recombinant human granulocyte colony-stimulating factor; COHNMC = City of Hope National Medical Center; FHCRC = Fred Hutchinson Cancer Research Center; MNIH = Montreal Neurological Institute and Hospital; MPE = methylprednisolone.
What causes remission?

Disability

Time

VLA-4

\(\alpha_4\)

\(\beta_1\)

Natalizumab
Disease activity return during natalizumab treatment interruption in patients with multiple sclerosis


Neurology 2011;76:1858; Prepublished online May 4, 2011;
DOI 10.1212/WNL.0b013e31821e7c8a

This information is current as of June 3, 2011

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://www.neurology.org/content/76/22/1858.full.html
Unadjusted annualized relapse rate
(+95% confidence interval)

Months of treatment interruption

Highly active n = 768 766 763 758 746 730 617 163
Non-highly active n = 178 178 178 177 174 170 147 35

HA on-study placebo ARR: 1.28
NHA on-study placebo ARR: 0.66

Increased frequency of CD4$^+$ CD25$^+$ regulatory T cells in the cerebrospinal fluid but not in the blood of multiple sclerosis patients
Loss of Functional Suppression by CD4\(^+\)CD25\(^+\) Regulatory T Cells in Patients with Multiple Sclerosis

Vissia Viglietta, Clare Baecher-Allan, Howard L. Weiner, and David A. Hafler

*Laboratory of Molecular Immunology, Center for Neurologic Diseases, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA 02115*

J. Exp. Med. © The Rockefeller University Press Volume 199, Number 7, April 5, 2004 971–979

Reduced suppressive effect of CD4\(^+\)CD25\(^{\text{high}}\) regulatory T cells on the T cell immune response against myelin oligodendrocyte glycoprotein in patients with multiple sclerosis

Jürgen Haas\(^1\), Andreas Hug\(^1\), Andrea Viehöver\(^1\), Benedikt Fritzsching\(^1,2\), Christine S. Falk\(^3\), Andrea Filser\(^1\), Tina Vetter\(^1\), Linda Milkova\(^1\), Mirjam Korporal\(^1\), Brigitte Fritz\(^1\), Brigitte Storch-Hagenlocher\(^1\), Peter H. Krammer\(^3\), Elisabeth Suri-Payer\(^2\) and Brigitte Wildemann\(^1\)
Characterization of a rare IL-10–competent B-cell subset in humans that parallels mouse regulatory B10 cells

*Yohei Iwata,¹ *Takashi Matsushita,¹ Mayuka Horikawa,¹ David J. DiLillo,¹ Koichi Yanaba,¹ Guglielmo M. Venturi,¹ Paul M. Szabolcs,¹,² Steven H. Bernstein,³ Cynthia M. Magro,⁴ Armistead D. Williams,⁵ Russell P. Hall,¹,⁶ E. William St Clair,¹,⁷ and Thomas F. Tedder¹

Departments of ¹Immunology and ²Pediatrics, Duke University Medical Center, Durham, NC; ³James P. Wilmot Cancer Center, University of Rochester School of Medicine and Dentistry, Rochester, NY; ⁴Department of Pathology and Laboratory Medicine, Weill Medical College of Cornell University, New York, NY; ⁵International Multiple Sclerosis Management Practice, New York, NY; and Departments of ⁶Dermatology and ⁷Medicine, Duke University Medical Center, Durham, NC
Conclusion

• During relapsing-remitting MS, clinical attacks are likely caused by lymphocytes.
Conclusion

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• Much of our knowledge on the immunology in relapsing-remitting MS stems from observations made with specific pharmacotherapies.
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• During relapsing-remitting MS, clinical attacks are likely caused by lymphocytes.

• Much of our knowledge on the immunology in relapsing-remitting MS stems from observations made with specific pharmacotherapies.

• There is an intricate interplay between many cellular subsets.
Conclusion

- CD4$^+$ T cells and B cells are thought to be key players in MS pathogenesis
Conclusion

• CD4$^+$ T cells and B cells are thought to be key players in MS pathogenesis

• Some T cells and B cells also have regulatory function
Conclusion

• CD4$^+$ T cells and B cells are thought to be key players in MS pathogenesis

• Some T cells and B cells also have regulatory function

• Regulatory cells may be used therapeutically
The End