Dysbiosis and Multiple Sclerosis: Influence of the Gut Microbiome on Autoimmune Disease

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Objectives

• Understand the pathophysiology of multiple sclerosis

• Recognize the complexity of the gut microbiome on our immune system

• Realize our gut bacteria can influence autoimmunity, multiple sclerosis

• Understand that disruptions in gut flora are associated with many diseases
Autoimmune Disease

- Multiple Sclerosis
- Rheumatoid Arthritis
- Type 1 diabetes, etc.
- Grave’s Disease
- Hemolytic Anemia
Multiple Sclerosis Plaques

Healthy brain

Brain with damage (lesions or plaques) caused by MS

Intermountain Medical Imaging, Boise, Idaho. Obtained from myhealth.alberta.ca
Progressive-relapsing multiple sclerosis
Steady decline since onset with super-imposed attacks.

Secondary progressive multiple sclerosis
Initial relapsing-remitting multiple sclerosis that suddenly begins to have decline without periods of remission.

Primary progressive multiple sclerosis
Steady increase in disability without attacks.

Relapsing-remitting multiple sclerosis
Unpredictable attacks which may or may not leave permanent deficits followed by periods of remission.
Current Treatments for MS

• To **treat** attacks
  – Corticosteroids

• To **prevent** relapse & slow progression
  – Glatiramer acetate
  – Beta interferons
  – Fingolimod
  – Natalizumab
  – Teriflunomide

Immunology Review
Antigen Presenting Cells (APC)

MICROBES ENTER THROUGH BREAK IN SKIN AND ARE PHAGOCYTOSED BY DENDRITIC CELL

activated dendritic cell activates T cells to respond to microbial antigens on dendritic cell surface

Activated T cells migrate to site of infection via the blood

remnants of microbe in phagolysosome

activated dendritic cell

lymph node

activated T cell

Regulatory T cells suppress pro-inflammatory cells.
T Cells Induce B Cell Activation

• T Cell and B Cell must recognize the same antigen presented

• Prevents autoimmunity
Multiple Sclerosis Pathophysiology

1. Innate
   Immature dendritic cell
   - TGFβ
   - IL-10

2. Adaptive
   Naive T cell
   - TGFβ
   - IL-4
   - IL-10

3. T_reg cell
   Macrophage
   - B cell
   - Blood-brain barrier

Unbalanced Inflammation in MS

Pro-Inflammation
- Th17
- Th1
- Th2
- M1 Macrophages
- IFNγ
- IL-17
- TNF
- IL-2
- IL-12

Anti-Inflammation
- Tregs
- M2 Macrophages
- IL-10
10 to 100 trillion organisms in gut

100+ different species

Outnumbered 10:1
The Human Microbiome Project

• Consortium of scientists
  – Sample and analyze the microbes throughout our body

• Still in progress…
  – Multiple papers have been published

Accessed at commonfund.nih.gov/hmp/
Developed Bacterial Tolerance

Bacteroides fragilis

- Produce Polysaccharide A (PSA)
- Induces Treg differentiation & production of anti-inflammatory IL-10
- Prevents expansion of pro-inflammatory Th17
- Non-PSA producing B. frag do not have this response

Can the gut affect the brain?
Experimental Autoimmune Encephalomyelitis (EAE)

- Mouse model
- Used to mimic human T-cell-mediated relapse-remitting MS
  - Caution: Multiple proposed etiologies of MS
- Induced by immunization with CNS antigens
  - Myelin proteins
- Pathogenic by coadministration with *M. tuberculosis* and/or pertussis toxin
SPF = Specific Pathogen Free Mice
GF = Germ Free Mice

GF have Minimal EAE Symptoms

• **Germ Free Mice**
  - Attenuated signs of disease
    • Not due to unresponsive T cells
  - Reduced inflammatory cytokines & cells

• **SPF Mice**
  - Increased infiltration of leukocytes in CNS
  - Greater myelin erosion

Inflammation & EAE symptoms

Treg Cells Increased in GF Mice

Germ Free

Specific Pathogen Free

Segmented Filamentous Bacteria

CNS Antigen

SPF = Specific Pathogen Free Mice
GF-SFB = Germ Free Mice with Seg. Filamentous Bacteria
GF = Germ Free Mice

Flora Influence Immune System

• Gut bacteria potentiate inflammation
  – Goes beyond local inflammation; affects CNS

• Gut bacteria impact the T-helper/Treg axis
  – Pro-inflammation vs. Anti-inflammation

• Provides a rationale that bacteria can exacerbate multiple sclerosis
Not Just Multiple Sclerosis

Allogeneic Transplant – Altered Flora

- New bone marrow from another person
- Use immuno-suppression
- Risk for infection
- Given antibiotics
Graft vs. Host Disease (GVHD)

- Dry eyes
- Oral lesions
- Nail dystrophy
- Skin sclerosis
- Deep sclerosis
- Bronchiolitis obliterans
- Loss of bile ducts
- Fascitis
- Skin ulcers
- Spectrum of manifestations in cGVHD

Autoantibodies
M-skeletal
Infections
Endocrine
Metabolism
Nutrition
Pain
Quality of life
Disability
GVHD: T Cell Mediated Attack

- T cells lead attack in GVHD
- Gut flora changes may impact T cell activity
- Increase GVHD risk

Antibiotic Use Changes Microflora and Increases Risk of Infection

9 fold increased risk of VRE

5 x increased risk of Gram neg bacteremia

Future Human Study in MS

- **Step 1**: Analyze fecal microbiota
- **Step 2**: Analyze T cell differences
- **Step 3**: Alter the flora of MS patients...
Case: Ways to Alter Flora

• KT has finished his course of oral vancomycin 125 mg for his C diff infection. Two weeks later he presents back with recurrent infection. Next intervention:

• A. Metronidazole
• B. Vancomycin higher dose
• C. Fidaxomicin
• D. Fecal Transplant
Fecal Transplants Cure *C. difficile* Infection

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Restores gut flora diversity, too

Case: Ways to Alter Flora

• KT has finished his course of oral vancomycin 125 mg for his C diff infection. Two weeks later he presents back with recurrent infection. Next intervention:
  • A. Metronidazolate
  • B. Vancomycin higher dose
  • C. Fidaxomicin
  • D. Fecal Transplant
Future Human Study in MS

• **Step 1**: Analyze fecal microbiota

• **Step 2**: Analyze T cell differences

• **Step 3**: Alter the flora of MS patients with fecal transplants
Pharmacy Involvement

• Create an FDA-approved novel “probiotic”
'Poop Pills' Cure Serious Gut Infections
October 3, 2013 (AP)

By MARILYNN MARCHIONE AP Chief Medical Writer

Hold your nose and don't spit out your coffee: Doctors have found a way to put healthy people's poop into pills that can cure serious gut infections — a less yucky way to do "fecal transplants." Canadian researchers tried this on 27 patients and cured them all after strong antibiotics failed to help.

It's a gross topic but a serious problem. Half a million Americans get Clostridium difficile, or C-diff, infections each year, and about 14,000 die. The germ causes nausea, cramping and diarrhea so bad it is often disabling. A very potent and pricey antibiotic can kill C-diff but also destroys good bacteria that live in the gut, leaving it more susceptible to future infections.

Recently, studies have shown that fecal transplants — giving infected people stool from a healthy donor — can restore that balance. But they're given through expensive, invasive procedures like colonoscopies or throat tubes. Doctors also have tried giving the stool through enemas but the treatment doesn't always take hold.

There even are YouTube videos on how to do a similar treatment at home via an enema. A study...
Pharmacy Involvement

• Create an FDA-approved novel “probiotic”

• Use bacteria-produced chemicals

Clinical?
Discussion

1. As a pharmacist, would you rather your patient receive a fecal transplant or multiple antibiotics?

2. Name a non-psychiatric disease not associated with inflammation.

3. Will gut flora research change the way we treat disease? How a pharmacist practices?
Ending Thoughts…

• We are the lesser organism on/in our body

• Complex interactions between our immune system & gut bacteria

• Altering our gut flora may contribute to inflammatory autoimmune disease

• Robust human trials are needed
References

References

Potential questions

• Why can’t we use antibiotics
  – Leads to more pathogenic bacteria

• Is this applicable since it is from GF mice
  – It demonstrates proof of concept for humans

• Should we have less microbial exposure/like a GF animal?
  – No because we cannot live in a GF world, the more we encounter and allow our immune system to “tolerate” the less it will overreact

• Why did the mice EAE resolve at 35 days?
  – Mimics a relapse-remitting MS model so symptoms should resolve.
Potential questions

• How do APCs present self antigen?
  – take up both foreign as well as self-proteins and structures and process them intracellularly to antigens that are subsequently presented in the context of major histocompatibility

• If we decrease proinflammation would that lead us to increased infection?
  – No. I may have overemphasized ANTI-inflammation. A better term would have been immunoregulation. This allows for just enough inflammation, then resolves.

• Where does the immature dendritic cell reside?
  – Likely cervical lymph