Go with your gut: the gut-joint axis

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April 27, 2018

Learning objectives:

- Appreciate the role of the microbiome in educating the immune response;
- Appreciate the potential contribution of the microbiome in rheumatic diseases, especially spondylitis.
Outline
- The Puzzle
- The Microbiome and the Role of HLA
- The Juxtaposition

Hugh O. McDevitt
Discoverer of Immune Response Genes

“this type of genetic control of specific immune responses may play an important role in susceptibility to a variety of diseases in both animals and man” SCIENCE, January, 1972.

High association of an HL-A antigen, W27, with ankylosing spondylitis.
- Schlosstein L, Terasaki PI,
- Bluestone R,
- Pearson CM
- N Engl J Med,
- 1973 Apr 5; 288(14):704-6
Reiter's disease and HL-A 27

Brewerton DA, Caffrey M, Nicholls A, Walters D, Oates JK, James DC

_Lancet_. 1973 Nov 3;302(7836):996-8

Also acute anterior uveitis

HLA B27 increases the risk of developing ankylosing spondylitis about 100 fold

- >700 HLA B alleles
- >105 HLA B27 subtypes
- HLA-B*2706 (southeast Asia) and HLA-B*2709 (Sardinia) do not predispose to disease

Human Leukocyte Antigens (HLA) vs GWAS

- HLA types influence susceptibility to more than 100 diseases.
- In most genome wide association studies on genetically complex, immune-mediated diseases, HLA alleles are the genes responsible for the highest odds ratio.
- The mechanism of HLA-disease association is usually a mystery.
- HLA polymorphism might relate to protection of the species against pathogens.
The Concept of the Microbiome

- Bacteria in our body outnumber the cells in our body.
- 99% of all the transcripts expressed in the body are derived from microbes.
- Only a fraction of the microbial world that we host is easily cultured.
- Without bacteria, no vitamin K and no immune system.

Hypothesis: Time for a gut check. HLA B27 predisposes to ankylosing spondylitis by altering the microbiome

- Rosenbaum, JT
- Davey, MP
- Arthritis & Rheumatism

Induction of Colonic Regulatory T Cells by Indigenous Clostridium Species

- Koji Atarashi et al.
- January 21, 2011
Ectopic colonization of oral bacteria in the intestine drives T_{H1} cell induction and inflammation

Science, October 20, 2017

Gut-residing segmented filamentous bacteria drive autoimmune arthritis via T helper 17 cells

Immunity, June 25, 2010

Does the microbiome contribute to the pathogenesis of ankylosing spondylitis?

Supporting Evidence: 1, 2, 3, & 4
1. Bacteria most clearly associated with reactive arthritis
   - Salmonella
   - Shigella
   - Yersinia
   - Campylobacter
   - Chlamydia

2. Nature
   - Endotoxin-induced uveitis in rats as a model for human disease
     J. T. Rosenbaum, H. O. McDevitt, R. B. Guss
     & P. R. Egbert
     Department of Medicine, Stanford University School of Medicine,
     Stanford University Medical Center, Stanford, California 94305

3. HLA-B27 related arthritis and bowel inflammation. Part 2. Ileocolonoscopy and bowel histology in patients with HLA-B27 related arthritis
   - Mielants et.al.
   - The majority of patients with ankylosing spondylitis or reactive arthritis have ileal inflammation, especially with peripheral joint involvement.
4. The germfree state prevents development of gut and joint inflammatory disease in HLA-B27 transgenic rats

Taurog, JD, et.al., 180: 2359, 1994.

HLA B27

MICROBIOME

ALTERED GUT PERMEABILITY

BACTERIAL TRANSLOCATION

SPONDYLOARTHRITIS

August 20, 2014
HLA-B27 shapes the intestinal microbiota in humans

![PcoA plot]

LEWIS Cecal Mucosa (all samples)

- WT
- B27
- B7

**HLA B27**

**MICROBIOME**

**ALTERED GUT PERMEABILITY**

**BACTERIAL TRANSLOCATION**

**SPONDYLOARTHRITIS**
**SALMONELLA-TRIGGERED REACTIVE ARTHRITIS**

Use of Polymerase Chain Reaction, Immunocytochemical Staining, and Gas Chromatography-Mass Spectrometry in the Detection of Bacterial Components from Synovial Fluid

Simo Nikkari, Kaisu Rantakokko, Päivi Ekman, Timo Möttönen, Marjatta Leirisalo-Reino, Miika Vihtela, Leena Lehtonen, Jari Jalava, Pirskko Kuitula, Kaisa Granfors, and Paavo Torvainen

Arthritis and Rheumatism, January, 1999

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**Gut Bacterial DNA Translocation is an Independent Risk Factor of Flare at Short Term in Patients With Crohn's Disease**

Ko Salminen, MD, PhD; Peter Espaa, MD, PhD; Oiva Luotonen, MD, PhD; Luukka Isolauri, MD, PhD; Marko Santti, MD, PhD; Vesa Leskinen, MD, PhD; Ville Voutilainen, MD, PhD; Jari Jalava, MD, PhD; Kaisa Granfors, MD, PhD; Pirskko Kuitula, MD, PhD; Leena Lehtonen, MD, PhD; Jari Kivelä, MD, PhD; Oiva Luotonen, MD, PhD; Marko Santti, MD, PhD; Ville Voutilainen, MD, PhD; Kaisa Granfors, MD, PhD; Pirskko Kuitula, MD, PhD; Leena Lehtonen, MD, PhD; Jari Kivelä, MD, PhD

- 288 patients
- 34% with detectable bacterial DNA in blood
- HR for flare if DNA present = 8.75
- American Journal of Gastroenterology, April, 2016

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**Graphs showing bacterial DNA translocation in the gut and ankle**

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Specific antibiotics prolong murine lupus survival

NZW X BXSB F1 Model with renal disease and ACLA

Antibiotic effect on autoantibodies
Detection of EG DNA in liver bx from 3 patients with SLE

Effect of vaccinating against EG

ANTIGEN-PRESENTING CELLS CONTAINING BACTERIAL PEPTIDOGLYCAN IN SYNOVIAL TISSUES OF RHEUMATOID ARTHRITIS PATIENTS COEXPRESS COSTIMULATORY MOLECULES AND CYTOKINES

INGRID A. SCHRIJVER, MARIE-JOSE MELIEF, PAUL F. TAK, MAARTEN P. HAZENBURG, and JON D. LAMAN
Do these observations have therapeutic implications?

- Global transfer of fecal microbiota
- Prebiotics/diet (?as a neonate)
- Transfer of specific microbes or microbial products
- Repair of intestinal permeability (?as by sulfasalazine)
- Immunization against specific bacteria

Patients with ankylosing spondylitis have been breast fed less often than healthy controls: a case–control retrospective study


Immunoglobulin A Coating Identifies Colitogenic Bacteria in Inflammatory Bowel Disease

Aug. 28, 2014
Perturbed mucosal immunity and dysbiosis accompany clinical disease in a rat model of spondyloarthritis

Asquith et al., Arthritis & Rheumatology, 2016, 68:2151

Unresolved questions:
Increased bowel permeability is not unique to AS. (e.g. IBD, diabetes)
Bacterial cell wall in the joint is not unique to AS.
☐ Do all leaky guts allow translocation of the same bacteria?
☐ Why doesn’t translocation cause arthritis more often?
☐ Do some bacteria translocate more readily?
☐ Are all bacteria equally arthritogenic?
The Promise of Poop

Fecal transplants offer hope for treating many diseases. But they need to be studied more scientifically, says one of the treatment’s pioneers.
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- Phoebe Lin
- Kimberly Ogle
- Lindsey Watson
- Bob Colbert
- Tejpal Gill
- Maxime Breban
- Matthew Schleisman

Conclusions:

- The gut microbiome might influence all immune-mediated diseases.
- HLA molecules are not the major driver of microbial diversity, but they do contribute.
- The gut microbiome is strongly implicated in HLA B27-associated disease.
- Bacterial translocation is a real phenomenon that might contribute to rheumatic diseases.