THE GUT, THE BUGS AND SPONDYLITIS

from basic research to an integrative approach

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INSTITUTE *for* SPECIALIZED MEDICINE
State-of-the-Art Integrative Care for Arthritis and Autoimmune Diseases

SPONDYLOARTHROPATHIES

The spondyloarthropathy family consists of the following entities:

- Ankylosing spondylitis
- Undifferentiated spondyloarthritis
- Reactive arthritis
- Psoriatic arthritis
- Spondyloarthritis associated with IBD
- Juvenile onset spondyloarthritis

ANKYLOSING SPONDYLITIS AND GUT

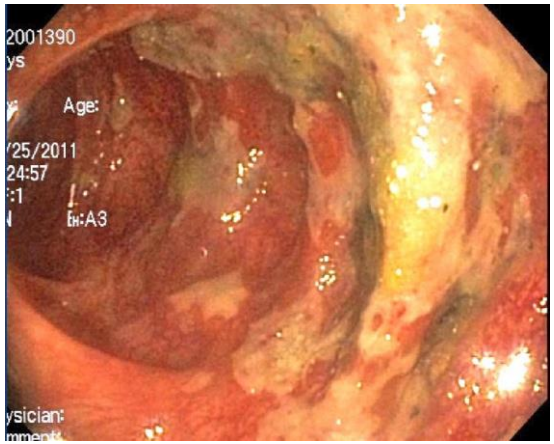
- Subclinical gut inflammation has been described in up to two-thirds of patients with spondyloarthropathies

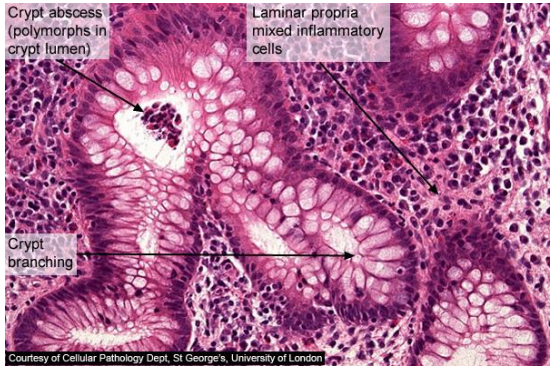
- Two histologic types of gut inflammation in patients with SpA can be distinguished: acute and chronic inflammation

ANKYLOSING SPONDYLITIS AND GUT

The **acute type** mimics the acute bacterial enterocolitis and is mainly seen in patients with **reactive arthritis**:

- The mucosal architecture is well preserved
- There is a polymorphonuclear infiltration of the ileal villi and crypts
- There is an increased number of inflammatory cells (granulocytes, lymphocytes and plasma cells) in the lamina propria



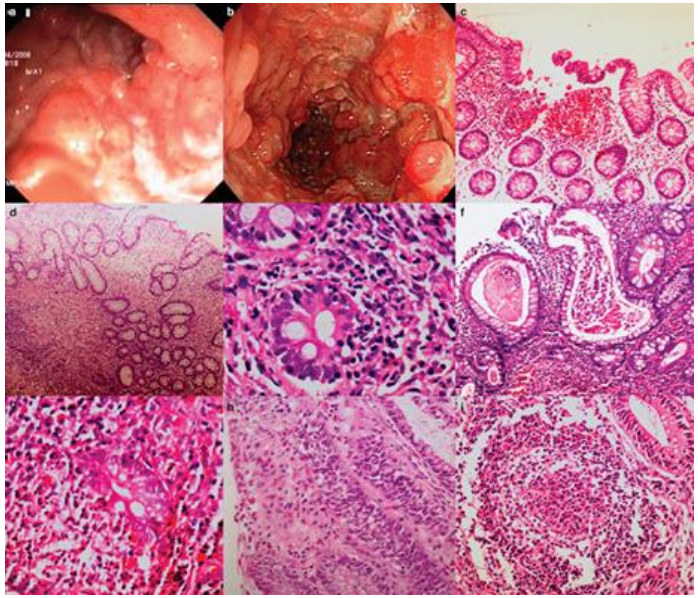


ANKYLOSING SPONDYLITIS AND GUT

The chronic type is often indistinguishable from Crohn's disease (CD):

- The mucosal architecture is clearly disturbed
- The villi are irregular, blunted and fused
- The crypts are distorted
- The lamina propria is edematous and infiltrated by mononuclear cells
- In some cases aphthoid ulcers and sarcoid-like granulomas are present

Chronic lesions are more present in undifferentiated SpA and AS.

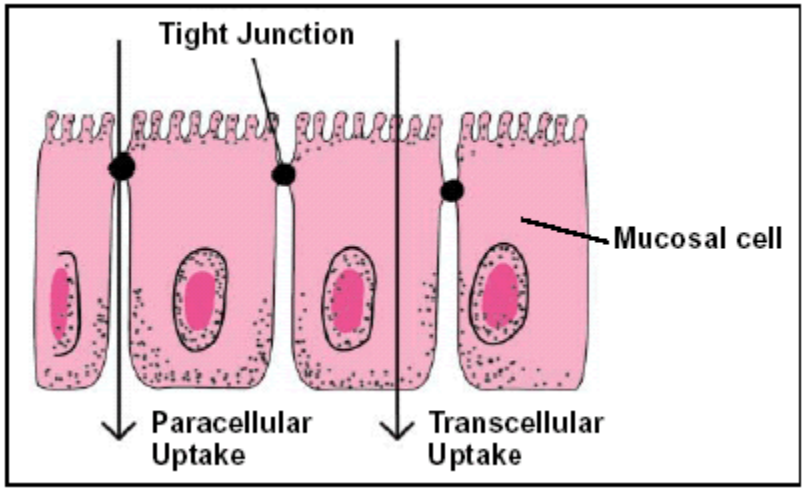


ANKYLOSING SPONDYLITIS AND GUT

- Increased intestinal permeability or leaky gut syndrome is a key mechanism contributing to the development and chronic course of ankylosing spondylitis and other autoimmune diseases and inflammatory arthritis.

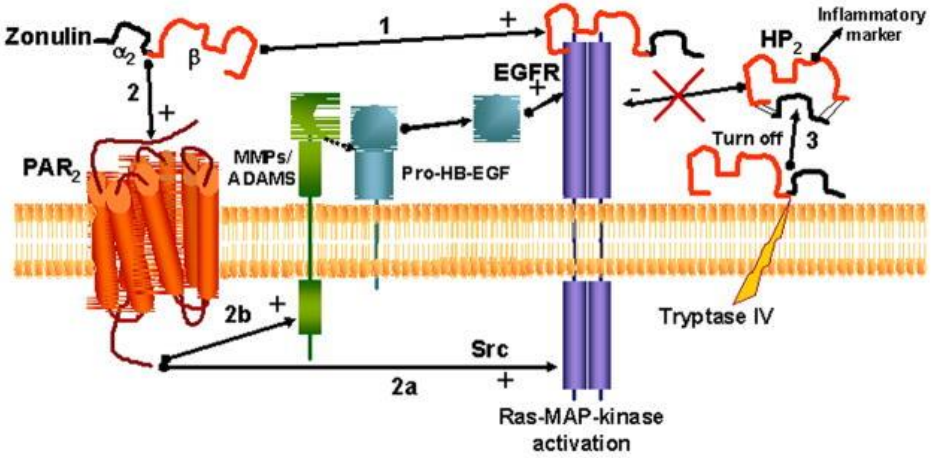
- The leaky gut allows substances such as toxins, microbial antigens, undigested food, waste, or larger than normal macromolecules to leak through an abnormally permeable gut wall and trigger cascades of inflammatory reactions.

Tight junctions (TJs) represent the major barrier within the pathway between intestinal epithelial cells that line the digestion tract



ANKYLOSING SPONDYLITIS AND GUT

- Zonulin is a protein regulating intestinal permeability via modulation of tight junction
- Small intestines exposed to enteric bacteria secrete zonulin
- This secretion occurs only on the luminal aspect of the bacteria-exposed small intestinal mucosa and is followed by an increase in intestinal permeability



ANKYLOSING SPONDYLITIS AND GUT

Mielants H, Veys EM, De Vos M, Cuvelier C. **Increased intestinal permeability in ankylosing spondylitis.** *Gut. 1992 Aug;33(8):1150.*

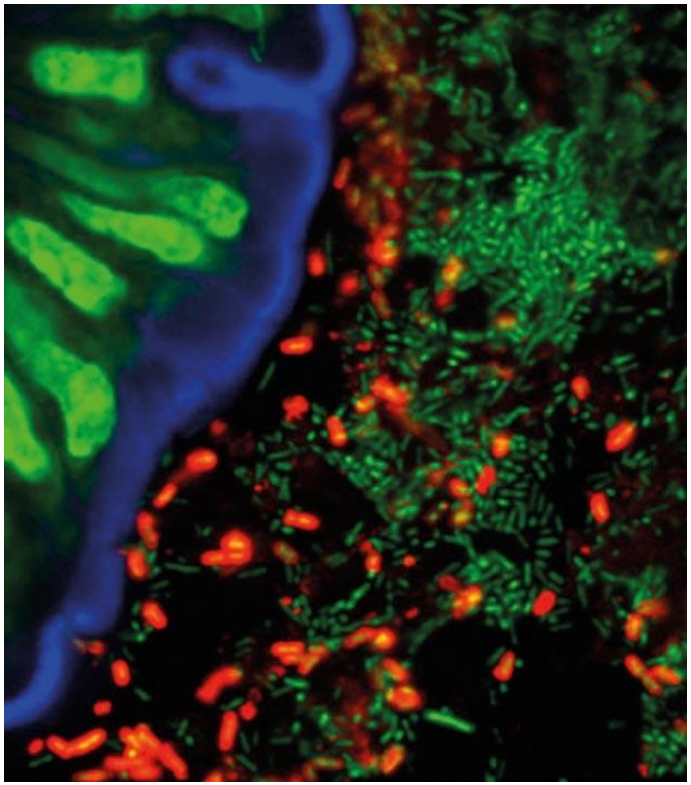
Martínez-González O, Cantero-Hinojosa J, Paule-Sastre P, Gómez-Magán JC, Salvatierra-Ríos D. **Intestinal permeability in patients with ankylosing spondylitis and their healthy relatives**. *Br J Rheumatol. 1994 Jul;33(7):644-7.*

Liu Y, Xu B, Cai X. **The role of intestinal permeability in the pathogenesis of ankylosing spondylitis.** *Zhonghua Nei Ke Za Zhi. 1995 Feb;34(2):91-4.*

Vaile JH, Meddings JB, Yacyshyn BR, Russell AS, Maksymowych WP. **Bowel permeability and CD45RO expression on circulating CD20+ B cells in patients with ankylosing spondylitis and their relatives.** *J Rheumatol. 1999 Jan;26(1):128-35.*

ANKYLOSING SPONDYLITIS AND GUT MICROBIOTA

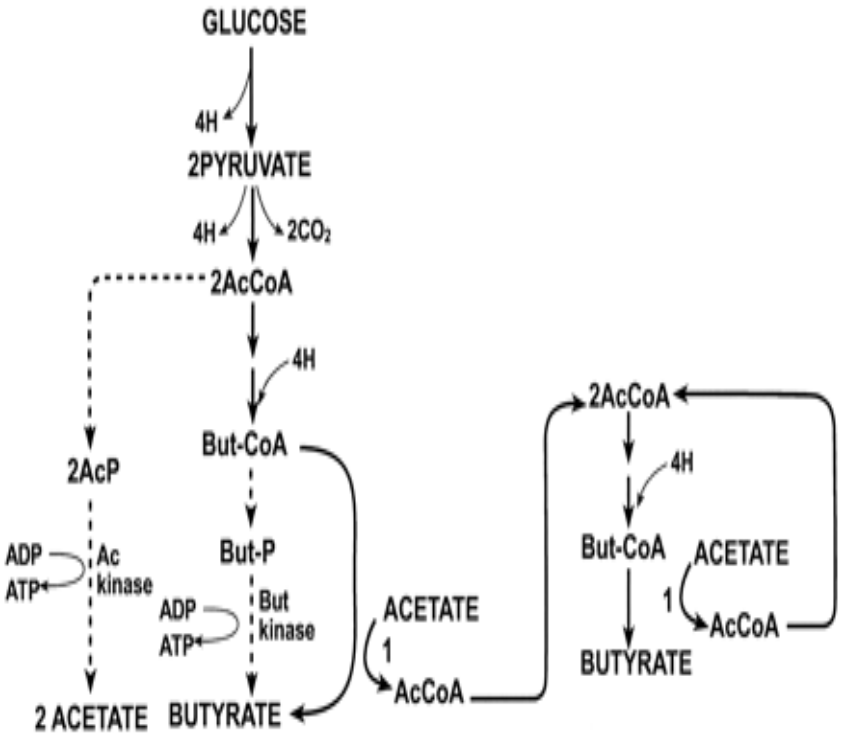
- Gut microbiota consists of a complex of microorganism species that live in the digestive tract
- The human body carries about 100 trillion microorganisms in its intestines, a number ten times greater than the total number of human cells in the body
- The metabolic activities performed by these bacteria resemble those of an organ, leading some to liken gut bacteria to a "forgotten" organ



ANKYLOSING SPONDYLITIS AND GUT MICROBIOTA

- Gut microbiota primary benefits the host by generating energy from the fermentation of undigested carbohydrates and the subsequent absorption of short chain fatty acids.

- The most important of these are butyrates, metabolized by the colonic epithelium and normalizing intestinal permeability.



ANKYLOSING SPONDYLITIS AND GUT MICROBIOTA

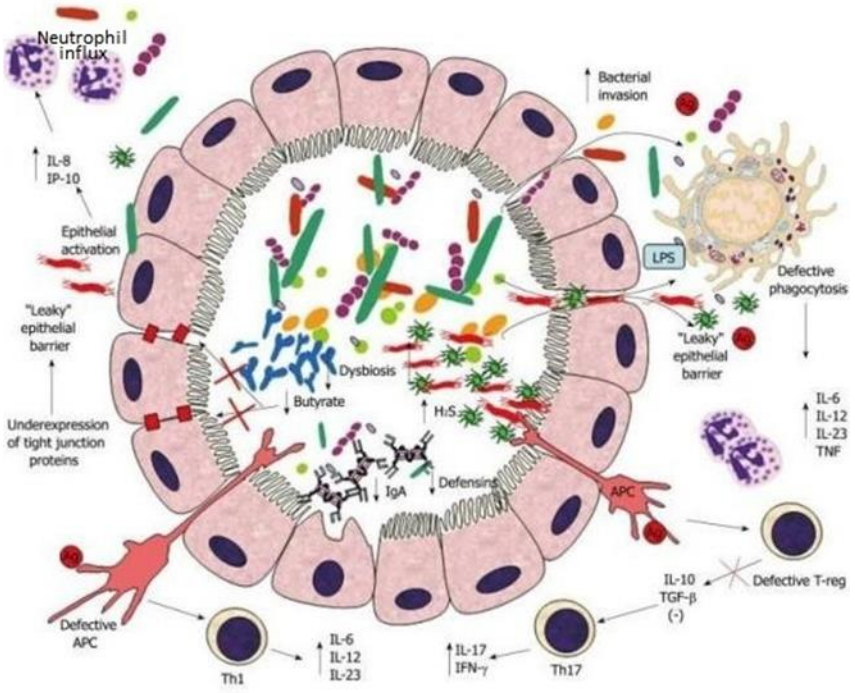
Ankylosing spondylitis (AS) - HLA-B27 association

- AS patients: >95% HLA-B27 positive
- <5% chance of AS if are HLA-B27 +
  - But family history of AS increases risk
- How does HLA-B27 cause disease:
  - fails to eliminate organism?
  - presents arthritogenic peptide?
  - Answer is not known

ANKYLOSING SPONDYLITIS AND GUT MICROBIOTA

THE HLA-B27 CONNECTION

- HLA B27 influences the composition of the body's endogenous flora and the 'B27-shaped flora' predisposes to ankylosing spondylitis
- HLA-B27 transgenic mice do not develop spondylitis-like lesions in germ-free environment
- Antibiotic therapy prevents spondylitis and colitis in HLA-B27 transgenic rats



ANKYLOSING SPONDYLITIS THERAPEUTIC GOALS

- NORMALIZATION OF INTESTINAL PERMEABILITY
- OPTIMIZATION OF GUT MICROFLORA
- OPTIMIZATION OF TOXIN REMOVAL
- REDUCTION OF LOCAL/MUCOSAL INFLAMMATION
- REDUCTION OF SYSTEMIC INFLAMMATORY RESPONSES AND PREVENTION OF ANKYLOSIS

NORMALIZATION OF INTESTINAL PERMEABILITY

- **BUTYRATE**

Peng L, Li ZR, Green RS, Holzman IR, Lin J. **Butyrate enhances the intestinal barrier by facilitating tight junction assembly via activation of AMP-activated protein kinase in Caco-2 cell monolayers**. J Nutr. 2009 Sep;139(9):1619-25.

- **L-GLUTAMINE**

dos Santos Rd, Viana ML, Generoso SV, Arantes RE, Davisson Correia MI, Cardoso VN. **Glutamine supplementation decreases intestinal permeability and preserves gut mucosa integrity in an experimental mouse model**. JPEN J Parenter Enteral Nutr. 2010 Jul-Aug;34(4):408-13.

- **BERBERINE**

Gu L, Li N, Gong J, Li Q, Zhu W, Li J. **Berberine ameliorates intestinal epithelial tight-junction damage and down-regulates myosin light chain kinase pathways in a mouse model of endotoxinemia**. J Infect Dis. 2011 Jun 1;203(11):1602-12

OPTIMIZATION OF GUT MICROBIOTA

- **PROBIOTICS**

live microorganisms which beneficially improve intestinal microbial balance

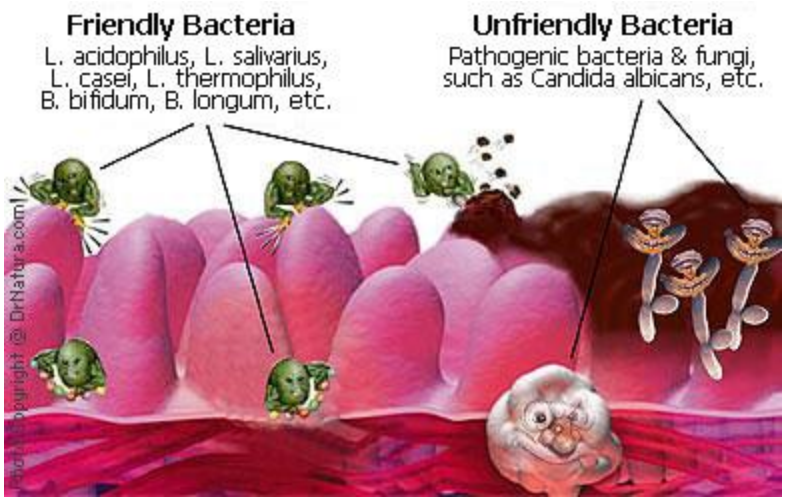
- **PREBIOTICS**

non-digestible polysaccharides that stimulate the growth and/or activity of ‘good’ bacteria in the digestive system

- **SYNBIOTICS**

nutritional supplements combining probiotics and prebiotics

- **BUTYRATE**
- **DIGESTIVE ENZYMES**



OPTIMIZATION OF GUT MICROBIOTA

CLINICAL TRIALS UTILIZING PROBIOTICS IN ANKYLOSING SPONDYLITIS

- limited number of published clinical trials
- insufficient number of participants to make any meaningful conclusions
- absence of reliable clinical or/and laboratory markers to measure the trials outcome
- poor clinical design (low dose of probiotics, poor selection of the probiotic strains)

OPTIMIZATION OF GUT MICROBIOTA

PROBIOTICS

- THE RIGHT DOSE
- THE RIGHT STRAIN(S)
- THE RIGHT TIME OF ADMINISTRATION
- SPACING OUT PROBIOTICS FROM ANTIBIOTICS AND DMARDs

OPTIMIZATION OF GUT MICROBIOTA

PREBIOTICS

- no published clinical trials
- experimental data utilizing beta-glucan and mannan-oligosaccharides based prebiotics demonstrated negative effect in animals with experimental colitis and Crohn’s disease

OPTIMIZATION OF GUT MICROBIOTA

DIETARY MODIFICATIONS

- Generic dietary approach (Mediterranean diet, anti-inflammatory diet, vegan diet etc) has low success rate
- Individualized elimination diet
- Based on our experience, we do see the best correlation with IgG4-based food intolerance testing system
- The IgG4-based food intolerance testing is performed in IFSMED lab
- The benefits of elimination diet are typically observed in 6-8 weeks

OPTIMIZATION OF GUT MICROBIOTA

DIGESTIVE ENZYMES

- enzymes of animal origin (pancreatic enzymes/pancreatin)
- plant-based enzymes
- medicinal mushrooms/medicinal molds-based enzymes

OPTIMIZATION OF TOXIN REMOVAL

- Calcium glucarate
- Psyllium/apple pectin
- Triphala
- Citrulline malate
- Acetyl-L-carnitine

REDUCTION OF LOCAL/MUCOSAL INFLAMMATION

TRADITIONAL THERAPY

- Sulfasalazine
- 5-ASA
- Corticosteroids

COMPLEMENTARY THERAPY

- Curcumin
- Boswellia
- Devil's claw
- Berberine
- N-acetylglucosamine
- Omega-3 polyunsatturated fatty acids
- Oral bovine immunoglobulins

REDUCTION OF SYSTEMIC INFLAMMATORY RESPONSES

TRADITIONAL THERAPY

- Biologics
- NSAIDs
- Sulfasalazine
- 5-ASA
- Corticosteroids

COMPLEMENTARY THERAPY

- Curcumin
- Boswellia
- Devil's claw
- Omega-3 polyunsatturated fatty acids

GUT-FOCUSED THERAPY IN ANKYLOSING SPONDYLITIS

TRADITIONAL THERAPY + COMPLEMENTARY THERAPY = INTEGRATIVE APPROACH

SULFASALAZINE + BUTYRATE/GLUTAMINE
+ BERBERINE

TRIPHALA + CALCIUM GLUCARATE + CITRULLINE MALATE

BACILLUS COAGULANS + DIGESTIVE ENZYMES
+ BOVINE IMMUNOGLOBULINS

OMEGA-3 + DEVIL'S CLAW + BOSWELLIA/CURCUMIN