SPONDYLOARTHROPATHIES: GUT MICROBIOME

American College of Osteopathic Internists (ACOI) Annual Mtg
October 12, 2023

Mary Hinojos Mamut, DO

DISCLOSURES

I have no disclosures.

PRACTICE GAP

Many physicians have a challenging time understanding the pathogenesis of spondyloarthropathies and the associated role of the gut microbiome. Recent research has identified connections between pathogenic pathways and gut microbiota, as well as dietary associations. Physicians should be aware of this emerging data so that it may help facilitate holistic, integrative treatment plans.

LEARNING OBJECTIVES

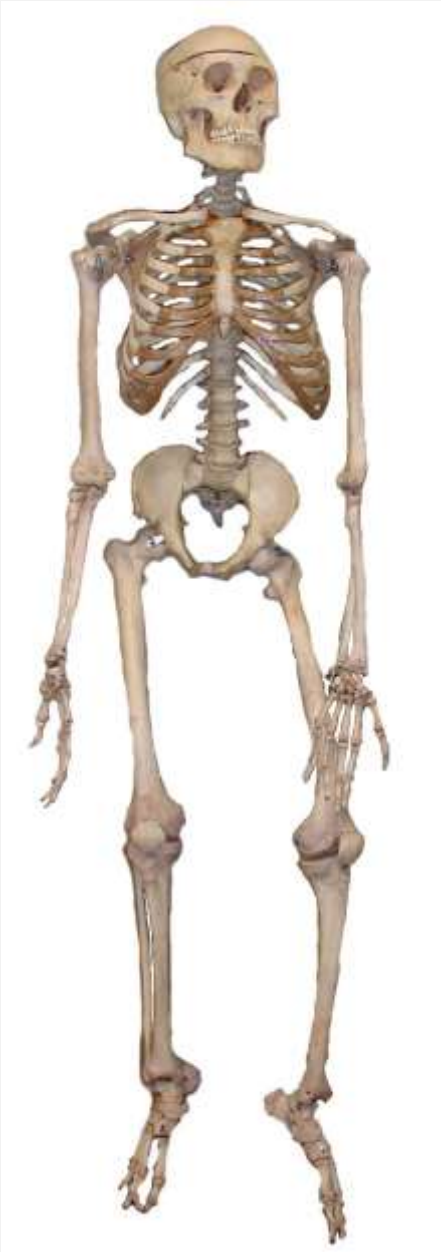
1. Discuss ongoing research in the field of spondyloarthropathies and the microbiome.
2. Describe unique findings of the gut microbiome in those with diagnosed spondyloarthropathies.
3. Design a care plan that incorporates an integrative approach to the treatment of those with spondyloarthropathies.

OVERVIEW OF SPONDYLOARTHROPATHIES

Understanding the Key Features and Classification

WHAT ARE SPONDYLOARTHROPATHIES?

- Spondyloarthropathies, also known as SpA, are a group of chronic inflammatory diseases primarily affecting the spine and other joints.
- These conditions share common clinical features and genetic predispositions.



CLASSIFICATION OF SPONDYLOARTHROPATHIES

- Ankylosing Spondylitis (AS)
  - Radiographic and non-radiographic
- Psoriatic Arthritis (PsA)
- Reactive Arthritis (ReA)
- Enteropathic Arthritis (associated with inflammatory bowel disease)
- Undifferentiated Spondyloarthropathy (uSpA)

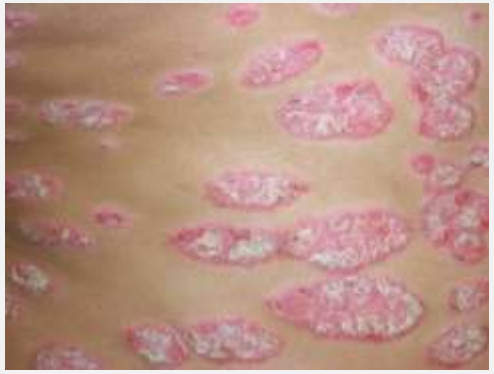
GENETIC PREDISPOSITION: HLA-B27

- Ankylosing Spondylitis (AS)
  - ~90% white pts and ~50-80% non-white pts
- Psoriatic Arthritis (PsA) (also HLA-Cw6, B38, B39, DR04)
  - ~50%
- Reactive Arthritis (ReA)
  - ~60-80% of pts
- Enteropathic Arthritis (associated with inflammatory bowel disease)
  - Crohn's ~55% and UC ~70%
  - IBD also HLA-B35, B44, B1*0103

West, S. G., & Kolfenbach, J. *Rheumatology secrets*. 2020

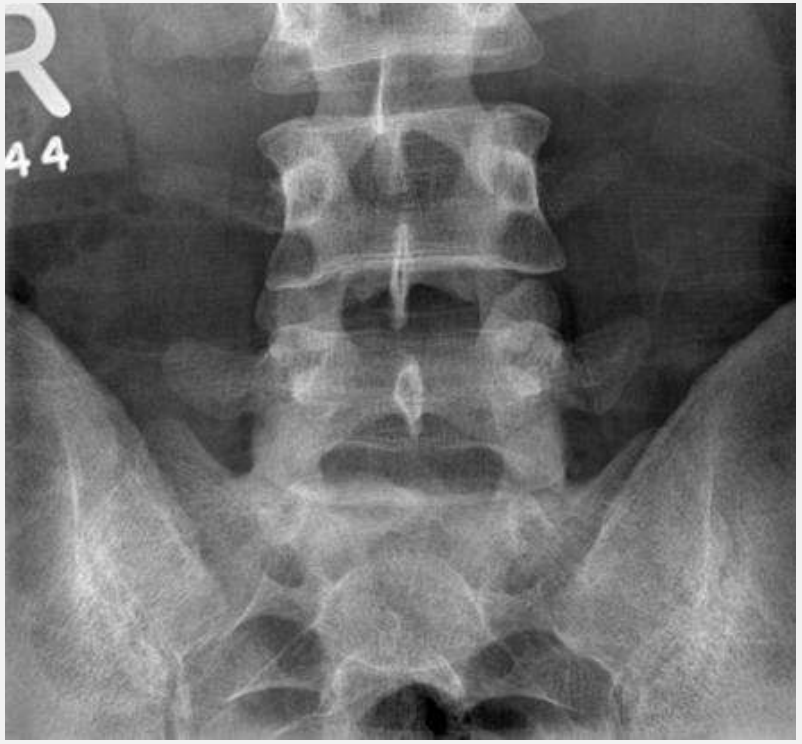
KEY FEATURES OF SPONDYLOARTHROPATHIES

- Inflammatory back pain: Chronic pain and stiffness in the lower back, often worse in the mornings and with rest.
- Enthesitis: Inflammation at the sites where tendons or ligaments attach to bones.
- Peripheral arthritis: Inflammation of joints, typically asymmetric and involving large joints (e.g., knee, ankle).
- Extra-articular manifestations: Involvement of other organs, such as the eyes, skin, and gastrointestinal tract.



DIAGNOSIS AND MANAGEMENT

- Diagnosis relies on a combination of clinical assessment, imaging (e.g., X-ray, MRI), and laboratory tests.
- Treatment aims to relieve symptoms, reduce inflammation, and improve overall quality of life.
  - Medications, physical therapy, exercise, and **LIFESTYLE** modifications.



MICROBIOME AND IMMUNITY

Human Gut

HUMAN MICROBIOME

- Humans carry 3-6 pounds of bacteria with approximately 3 million protein coding genes.
- Intestinal microbiome significantly differs from that of skin or GU.
- Intestinal microbes assist in degrading complex polysaccharides from diet and extract vitamins and amino acids.
- Intestinal microbiome may help maintain homeostasis when healthy OR promote inflammation in dysbiosis.

Scher JU et al., *Arthritis Rheumatol*. 2016

GUT MICROBIOME IN AUTOIMMUNITY

- The 20th century
  - Carl Waden – "toxemic factor hypothesis"
- More recent reports solidified the idea that gut infecting bacteria may cause distal arthritis
  - Reactive arthritis, IBD-related arthritis and SpA
  - Whipple's disease
  - Jejunoileal-bypass surgery

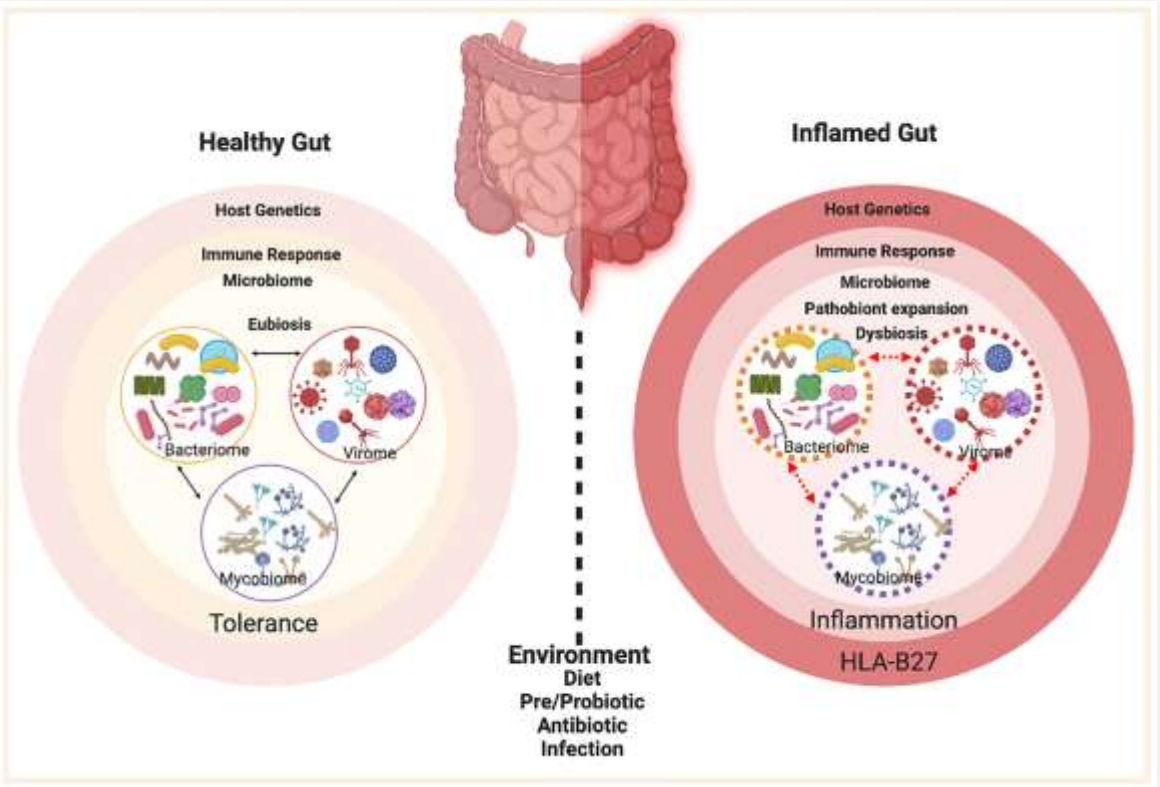
Scher JU et al., *Arthritis Rheumatol*. 2016

West, S. G., & Kolfenbach, J. *Rheumatology secrets*. 2020

GUT MICROBIOME

Factors Affecting the Gut Microbiome

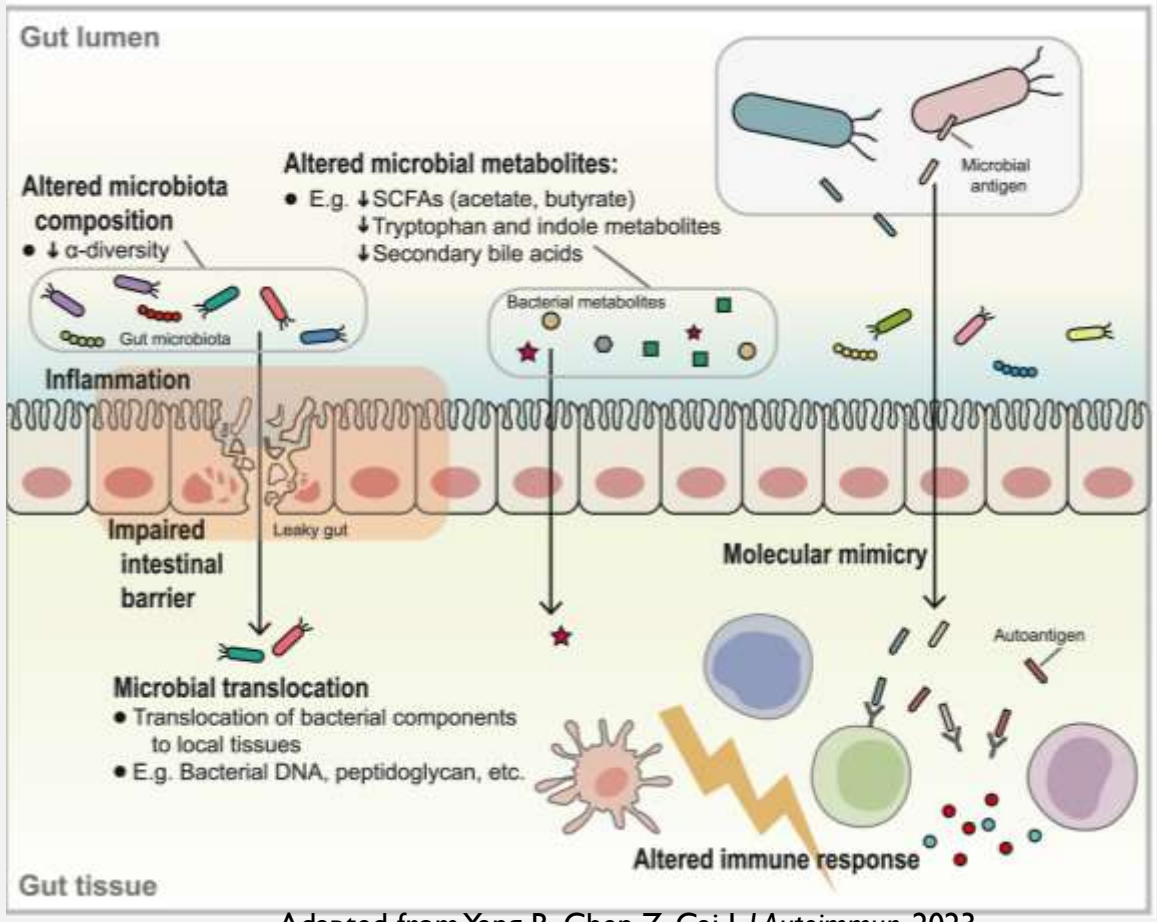
- Diet: High-fiber vs. low-fiber diets, plant-based vs. animal-based diets, etc.
- Medications: Antibiotics, proton pump inhibitors, etc.
- Lifestyle: Stress, exercise, sleep patterns, etc.
- Environmental factors: Exposure to pollutants, sanitation, etc.



Qin, J., et al. *Nature.* 2010
Sender, R., et al. *PLoS Biology.* 2016
Marchesi, J. R., et al. *Gut.* 2016
Lynch, S. V., & Pedersen, O. *New England Journal of Medicine.* 2016

GUT MICROBIOME

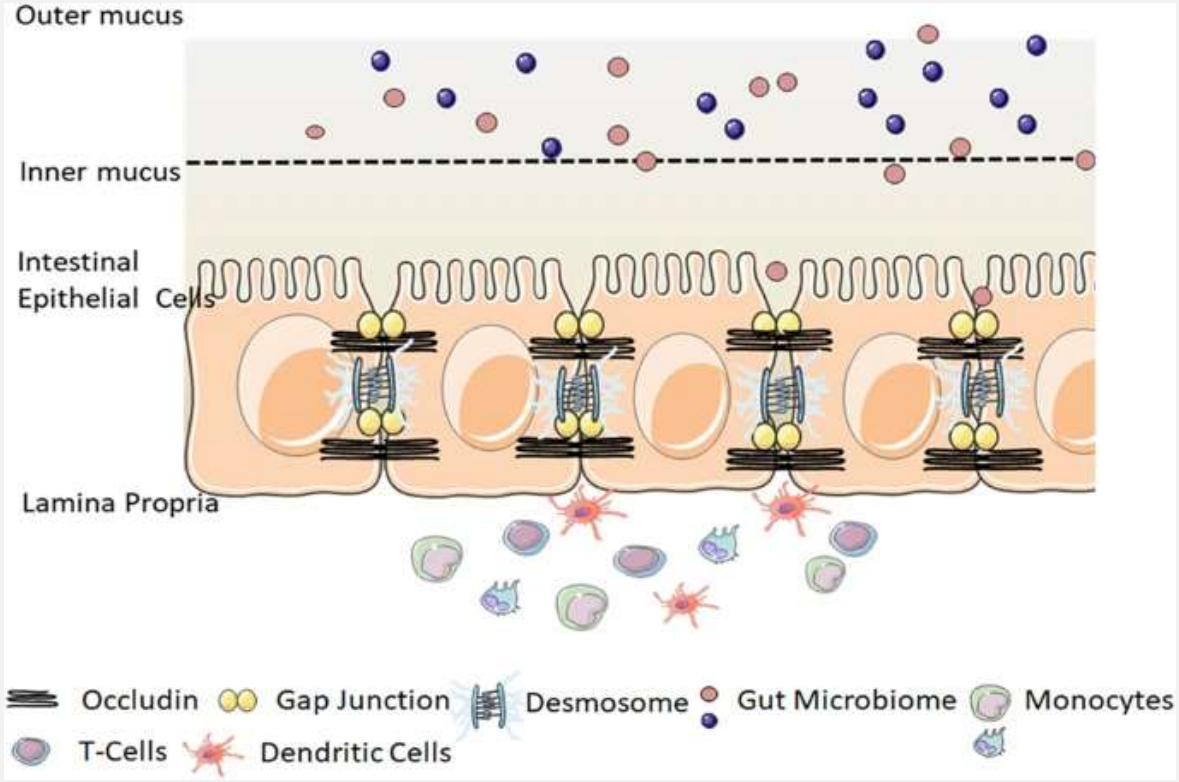
- Mechanisms of disruption
  - Impaired barriers
  - Changes in microbial translocation
  - Disruption of microbiota-derived metabolites
  - Molecularly mimicry
  - Dysregulation of immune cells



Adapted from Yang R, Chen Z, Cai J. *J Autoimmun.* 2023

IMMUNITY

- Mucus layer, antimicrobial protein and secretory IgA.
- Intestinal epithelial cells/mechanical barrier – pathogen-associated molecular patterns (PAMPs), such as toll-like receptors (TLRs) and antibacterial molecules.
- Innate immune cells, such as macrophages and dendritic cells (DCs).



Chelakkot, C., Ghim, J. & Ryu, S.H. *Exp Mol Med.,* 2018

Scher JU et al., *Arthritis Rheumatol*. 2016

IMMUNITY

- Antigens are presented by MHCII and interact with B and T cells receptors -> adaptive immune response
- The microbial antigen then determines the specific cytokine setting -> specific CD4+ T cell differentiation
- T helper 1 (Th1) cells triggered by intracellular pathogens -> IFN gamma
- Th2 and Th17 stimulated by extracellular pathogens -> IL-4 and IL-17
- Regulatory T cells (Tregs) generate anti-inflammatory IL-10

Scher JU et al., *Arthritis Rheumatol*. 2016

GUT AND CURRENT THERAPIES

- Sulfasalazine (designed to combine sulfa antibiotic with salicylate via an azo-bond)
  - FDA-approved in the treatment of RA, IBD and AS
- Hydroxychloroquine
- Tetracyclines (OFF LABEL)

Scher JU et al., *Arthritis Rheumatol*. 2016

SPA GUT

Animal Models

ANIMAL MODELS

- Hammer RE et al. described SpA-like disease in transgenic rats with HLA-B27 and human copies of beta-2 macroglobulin.
- Taurog JD, Richardson JA, Croft JT, et al. germfree rats failed to develop inflammatory bowel or joint disease.
- Germ-free mice over expressing TNF did not develop ileitis
- HLA-B27 rats colonized with *Bacteroides* developed inflammation, suggesting certain species may initiate.
  - Theorized due to HLA-B27 misfolding and activation Th17 cells, as well as IL-23

Hammer RE, et al. *Cell,* 1990.
Taurog JD, Richardson JA, Croft JT, et al. *The Journal of experimental medicine.* 1994
Scher JU et al., *Arthritis Rheumatol*. 2016

ANIMAL MODELS

- ANKENT (ankylosing enthesopathy) mouse model demonstrated HLA-B27 mice spontaneously develop progressive enthesitis and ankylosis triggered by commensals.
- SKG model, mice received systemic injection of B-glucan and developed SpA-like disease.
  - Severity of arthritis and ileitis dependent on host microbiome and IL-23-dependent IL-17/IL-22 production.
  - Mice with overexpressed IL-23 develop enthesis and osteoproliferation.

Sinkorova Z, Capkova J, Niederlova J, Stepankova R, Sinkora J., *Human immunology*. 2008
Scher JU et al., *Arthritis Rheumatol*. 2016
Ruutu M, Thomas G, Steck R, et al., *Arthritis and rheumatism*. 2012.
Rehaume LM, Mondot S, Aguirre de Carcer D, et al., *Arthritis & rheumatology*. 2014

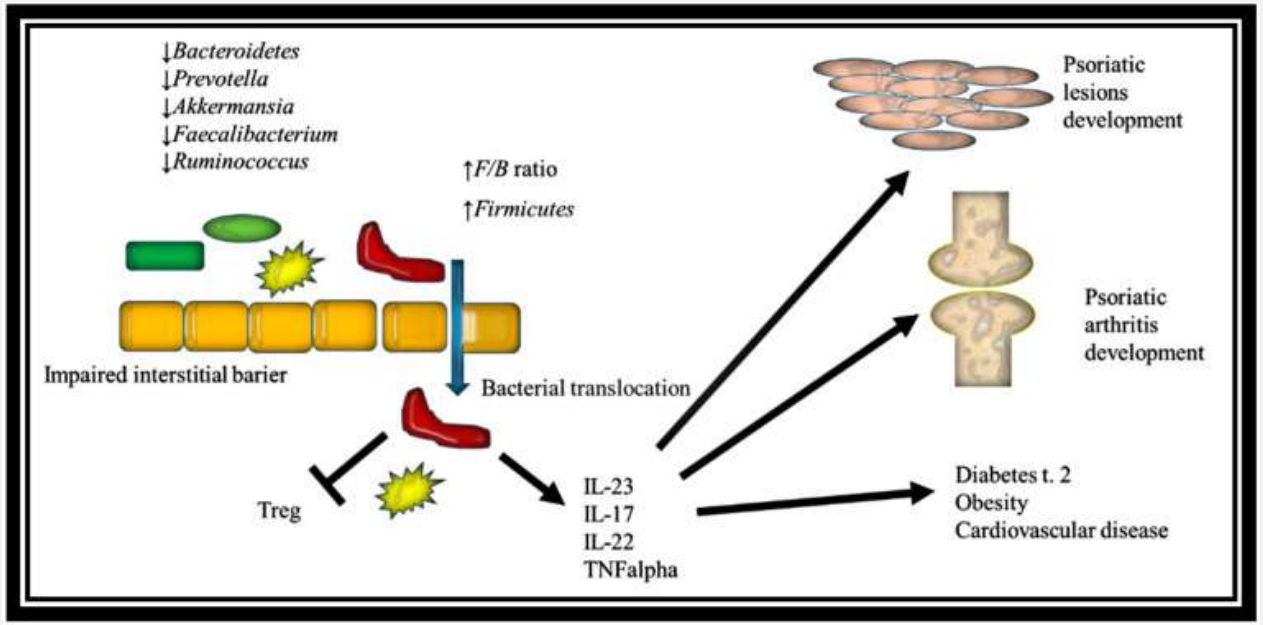
SPA GUT

- Asquith et al. (2014) collected stool samples from individuals with AS (n=43), RA (n=26), and healthy controls (n=61).
- Performed bacterial 16S rRNA gene sequencing and HLA genotyping.
- AS and RA patients had altered gut microbial communities compared to healthy controls.
- HLA alleles were associated with increased risk of AS (HLA-B27) or RA (HLA-DRB1) were linked to specific alterations in the gut microbiome.
- Suggest a potential interplay between genetic factors (HLA alleles) and the gut microbiome in the development or progression of spondyloarthropathies.

Asquith M, et al. *Arthritis Rheumatol.* 2019

SPA GUT

- Olejniczak-Staruch I, et al. 2021 review demonstrated the role of intestinal dysbiosis in PsA, as well as PsO.



Olejniczak-Staruch I, et al., *Int J Mol Sci.* 2021

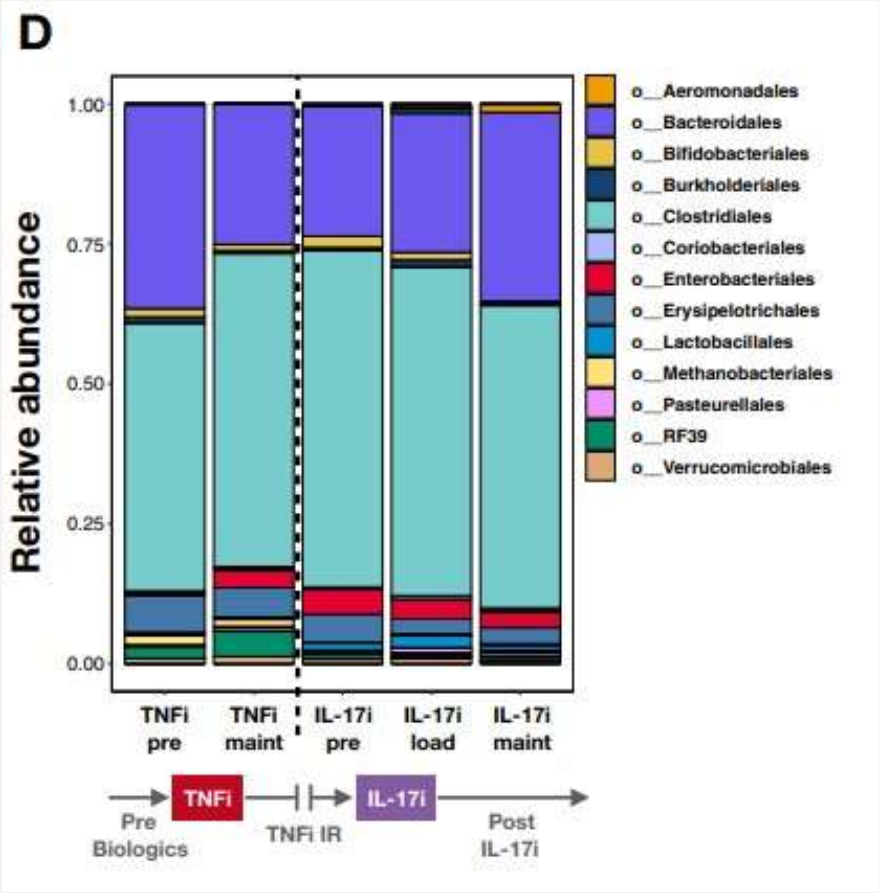
SPA MICROBIOME

- HLA-B27 transgenic rats vs wild-type controls
  - Increased *Prevotella spp.*
  - Decreased *Rikenellaceae* and *Akkermansia*
- AS patients
  - Increased *Lachnospiraceae* and *Prevotellaceae* in AS
  - Decreased *Ruminococcaceae* and *Rikenellaceae*
- PsA patients
  - Decreased *Ruminococcus* and *Akkermansia*
  - Decreased medium chain fatty acids (MCFAs) and RANKL
- IBD
  - Decreased *Ruminococcus* and *Akkermansia*

Scher JU et al., *Arthritis Rheumatol*. 2016

BACTERIAL ABUNDANCE W/ TX

- Bacterial abundance in PsA/SpA patients pre and post treatment with either TNFi of IL-17i
- TNFi cohort fecal samples collected at baseline and 6 months after initiating therapy
- IL-17i cohort samples collected at baseline, 5 weeks and 3 months



Manasson J, et al., Arthritis Rheumatol. 2020

Adapted from Manasson J, et al., Arthritis Rheumatol. 2020

SPA AND INFLAMMATORY BOWEL

- AS and PsA at risk of developing IBD (and visa versa)
  - Significant amount with subclinical GI inflammation (increased IL-22 and IL-23)
- Sulfate-reducing bacteria more prevalent in AS patients.

Scher JU et al., *Arthritis Rheumatol*. 2016

SPA GUT CONCLUSIONS

- Strongly suggests that genetic predisposition AND dysbiosis of the intestinal microbiome may lead to an immune response triggering a proinflammatory state in the lamina propria.
  - Production IL-23, activation of T cells, IL-17 and TNF alpha
  - Inhibition of T regs

MICROBIOME TREATMENT

ANTIBIOTICS

- Broad spectrum antibiotics as anti-rheumatic treatment have not demonstrated efficacy.
- Evidence has provided varying information in regards antibiotics potentially restoring dysbiosis.

Scher JU et al., *Arthritis Rheumatol*. 2016

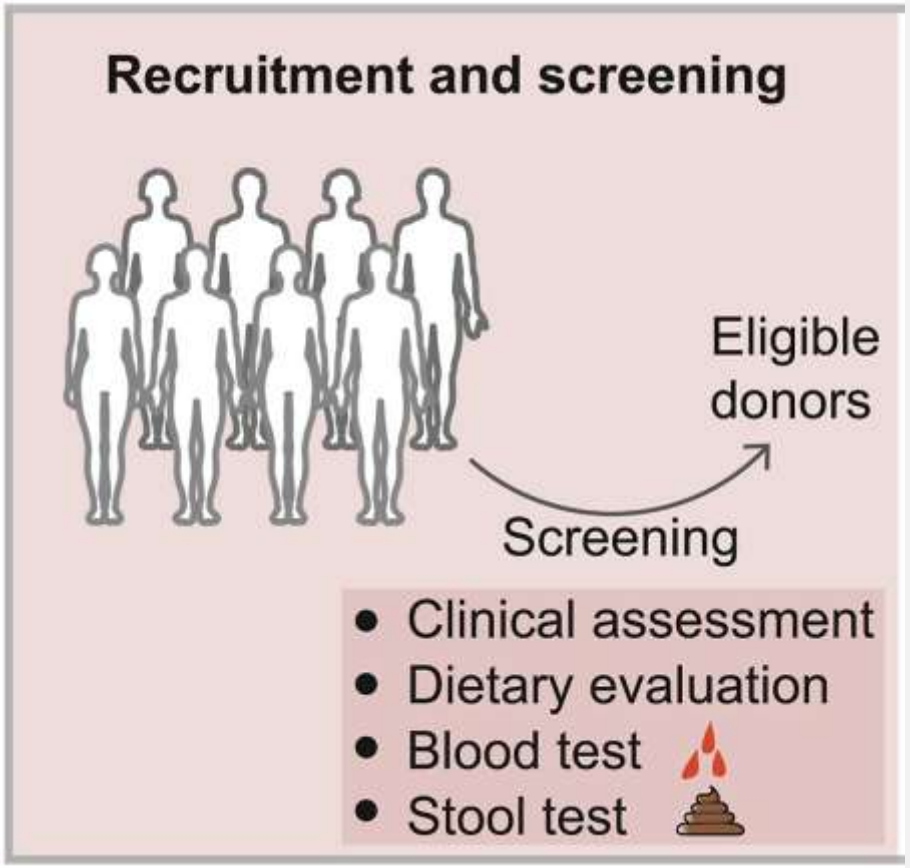
FECAL MICROBIAL TRANSPLANT (FMT)

- First report of fecal transplant is from traditional Chinese medicine book from 1700s.
- Goal is to transplant functional microbiota of donor feces into the GI tract of patient with dysbiosis of their gut microbiome.
- FMT has the potential to revert an altered microbiome to a balanced state.
- In modern reports, FMT is known for its efficacy treating *C. difficile*.
- Aside from the bacteria –
  - Bacteriophages and soluble components (such as microbiota metabolites) may also play a role in treatment.

Yang R, Chen Z, Cai J. *J Autoimmun*. 2023

FMT

- Donor selection crucial
  - Health questionnaires, clinical evals, stool and blood testing
- Donor selection process currently based on expert consensus
- Sequencing and computational approaches to identify specific donor traits
- Recruiting is challenging, criteria increasingly strict
- Autologous shown success in T1DM

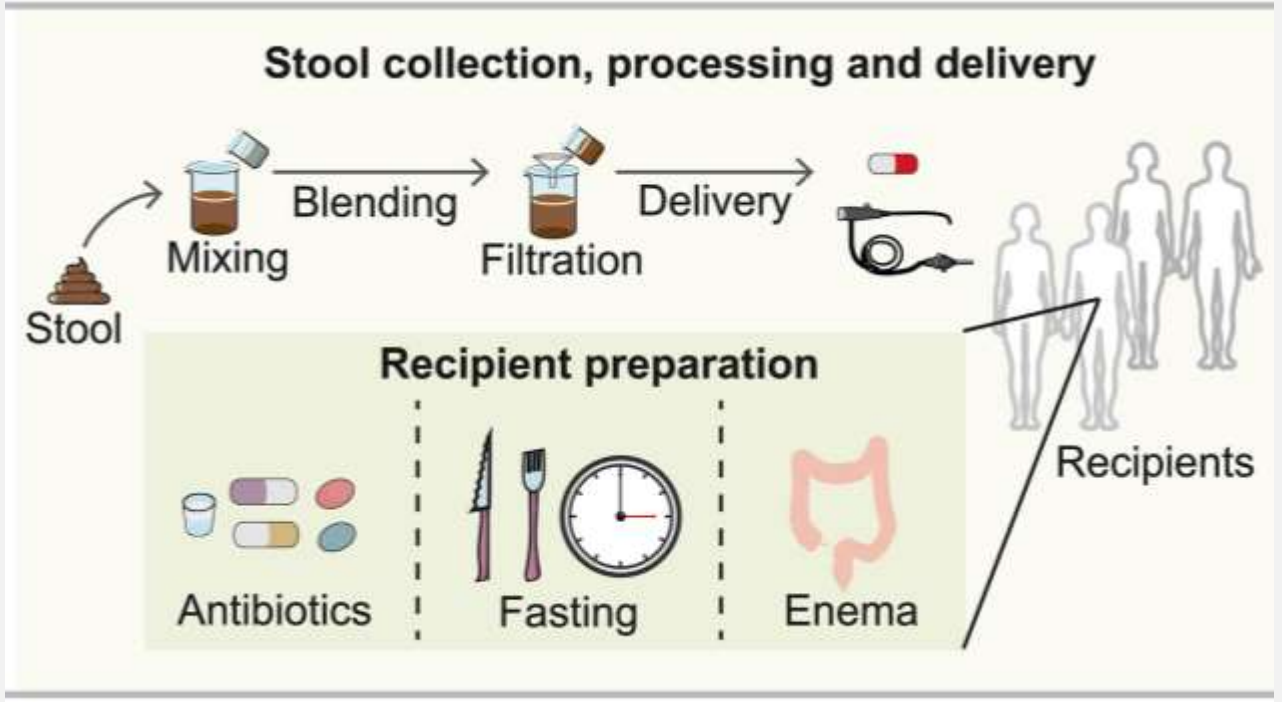


Adapted from Yang R, Chen Z, Cai J. *J Autoimmun*. 2023

Yang R, Chen Z, Cai J. *J Autoimmun*. 2023

FMT

- Steps: suspension, blending, filtration and storage; 50% bacteria non-viable
- NG tubes, NJ tubes, endoscopies, colonoscopies, and retention enemas
- Capsules: oral freeze-dried, encapsulated fecal microbiota -> potential for higher viability, engraftment and treatment efficacy



Yang R, Chen Z, Cai J. *J Autoimmun*. 2023

Adapted from Yang R, Chen Z, Cai J. *J Autoimmun*. 2023

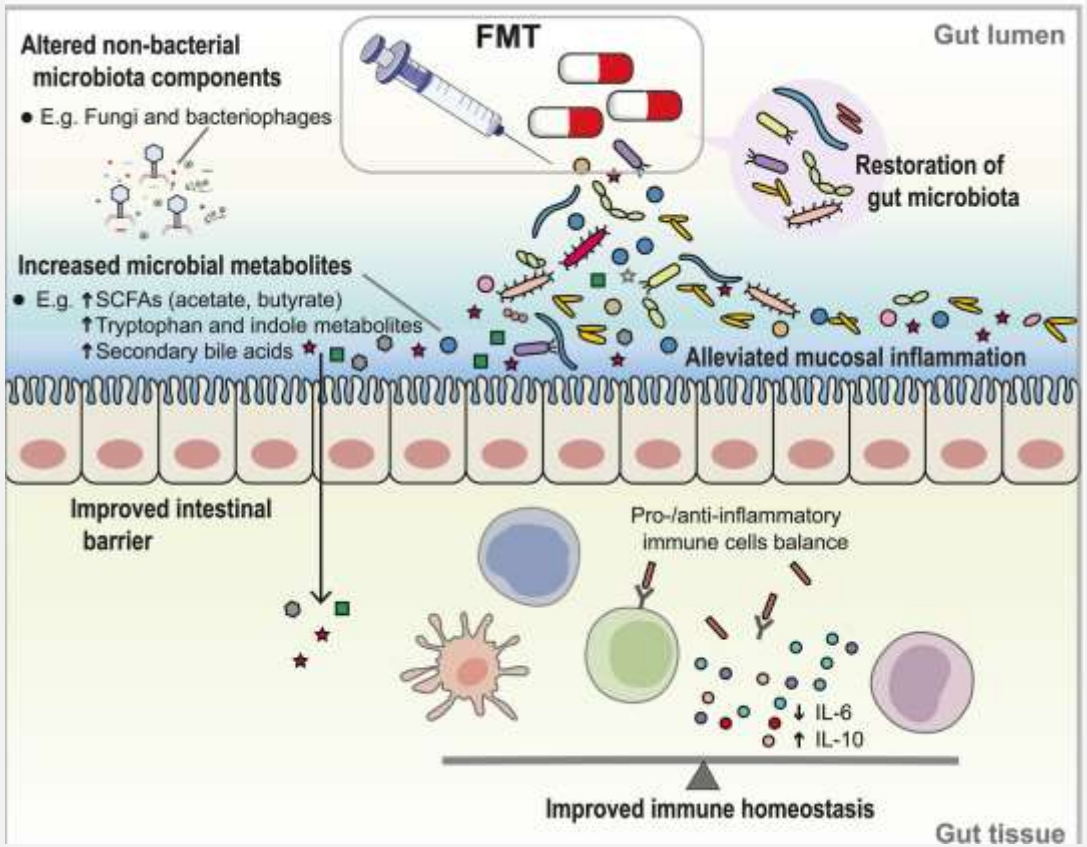
FMT

- Recipient success factors
  - Genetics, immune status, lifestyle, diet, smoking status, alcohol consumption, and medications
  - Donor-recipient microbiome interaction, donor-recipient relationship, microbial abundance
- Bioinformatics tools, such as Strain Finder -> ID and trace successful engrafted bacteria post-FMT

Yang R, Chen Z, Cai J. *J Autoimmun*. 2023

FMT

- Restoring the microbiome
  - Composition and function
  - Improved barrier function
  - Reduces inflammation of mucosa
  - Increase microbiota metabolites (such as SCFA, etc.)
  - Non-bacterial components (such as bacteriophages)
  - Improves immune homeostasis

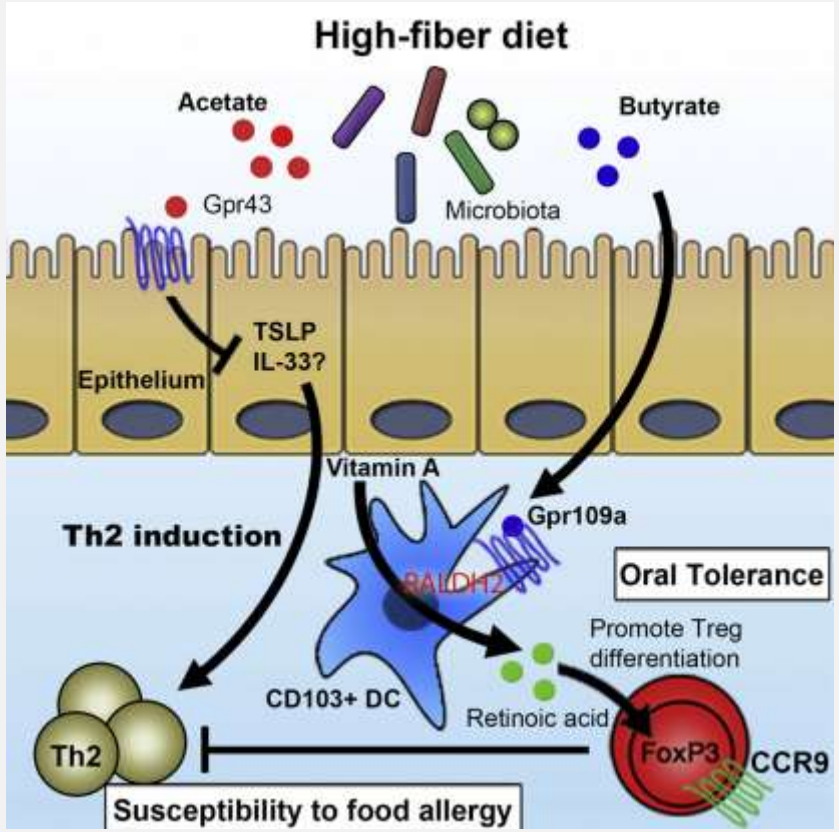


Yang R, Chen Z, Cai J. *J Autoimmun.* 2023

Adapted from Yang R, Chen Z, Cai J. *J Autoimmun.* 2023

DIET AND SUPPLEMENTS

- Anti-inflammatory diet
  - Pro-inflammatory: processed carbohydrates, red meat, sweetened beverages/sugar and saturated fats
- High fiber diet
- Prebiotics (SCFA, butyrate)
- Probiotics
- Omega-3
  - Decrease CRP and IL-6



Jian Tan et al. *Cell Reports*. 2016

Haidmayer A et al., *Nutrients*, 2020
Tajik N, et al., *Nature Commun,* 2020
Dürholz K et al., *Nutrients*, 2020
Eder L., et al., *Arthritis Rheumatol.* 2022 (ACR 2022)
Scher JU et al., *Arthritis Rheumatol.* 2016

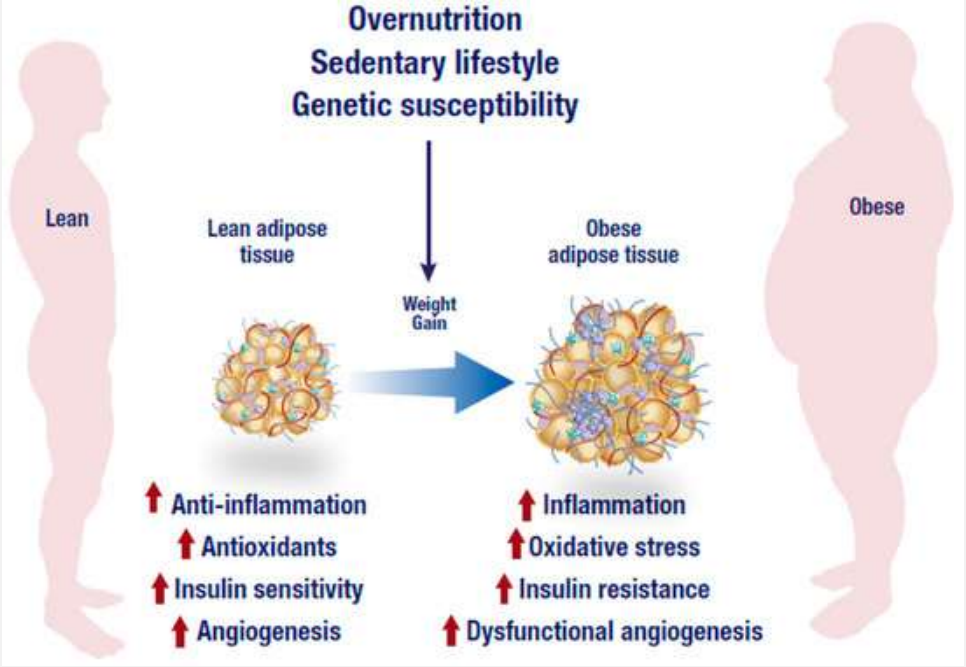
ANTI-INFLAMMATORY DIET

- Mediterranean diet
  - Focus on fruits, vegetables, whole grains, legumes, olive oil and fish (omega 3 fatty acids)
  - Minimize sugar, highly processed foods and meats, fast food, food high in trans-fat and saturated fat

Smedslund G, Byfuglien MG, Olsen SU, Hagen KB. J Am Diet Assoc. 2010

EXERCISE AND WEIGHT LOSS

- Associated link between psoriasis (PsO)/PsA, obesity and metabolic syndrome
- Obesity is an inflammatory state.
  - Adipose tissue releases TNFα and IL-6
  - Decrease release of adiponectin
    - => pro-inflammatory state/oxidative stress
- Obesity is associated with higher disease activity.
- Obesity decreases efficacy of TNFi.
- Pro-inflammatory cytokines contribute to an increased cardiovascular risk.



Dludla, P. et al., *Nutrients* 2019

Azevedo S, et al., *Acta Reumatol Port.*, 2019
Moroni L, et al., *Clin Rheumatol.,* 2020
Ellulu MS, et al., *Arch Med Sci.* 2017
Paine A, et al., *Arthritis Rheumatol.* 2023

SUMMARY

SUMMARY

- The intestinal microbiome likely plays a role in SpA immune expression.
- Treatment of gut microbiome dysbiosis is promising for therapy of SpA and other autoimmune diseases. Ongoing and further research is appreciated.
- There is evidence for integrative medicine in patients with autoimmune disease (as well as other chronic disease).

REFERENCES

- Hammer RE, Maika SD, Richardson JA, Tang JP, Taurog JD. Spontaneous inflammatory disease in transgenic rats expressing HLA-B27 and human beta 2m: an animal model of HLA-B27- associated human disorders. Cell. 1990; 63:1099–112. PMID: 2257626
- Taurog JD, Richardson JA, Croft JT, et al. The germfree state prevents development of gut and joint inflammatory disease in HLA-B27 transgenic rats. The Journal of experimental medicine. 1994; 180:2359–64. PMID: 7964509
- Scher JU, Littman DR, Abramson SB. Microbiome in Inflammatory Arthritis and Human Rheumatic Diseases. Arthritis Rheumatol. 2016 Jan;68(1):35-45. doi: 10.1002/art.39259. PMID: 26331579; PMCID: PMC4789258.
- West, S. G., & Kolfenbach, J. (2020). 36. In *Rheumatology secrets* (pp. 298–307)., Elsevier.
- Sinkorova Z, Capkova J, Niederlova J, Stepankova R, Sinkora J. Commensal intestinal bacterial strains trigger ankylosing enthesopathy of the ankle in inbred B10.BR (H-2(k)) male mice. Human immunology. 2008; 69:845–50. PMID: 18840492
- Ruutu M, Thomas G, Steck R, et al. beta-glucan triggers spondylarthritis and Crohn's disease-like ileitis in SKG mice. Arthritis and rheumatism. 2012; 64:2211–22. PMID: 22328069
- Rehaume LM, Mondot S, Aguirre de Carcer D, et al. ZAP-70 genotype disrupts the relationship between microbiota and host, leading to spondyloarthritis and ileitis in SKG mice. Arthritis & rheumatology. 2014; 66:2780–92. PMID: 25048686
- Jian Tan, Craig McKenzie, Peter J. Vuillermin, Gera Goverse, Carola G. Vinuesa, Reina E. Mebius, Laurence Macia, Charles R. Mackay, Dietary Fiber and Bacterial SCFA Enhance Oral Tolerance and Protect against Food Allergy through Diverse Cellular Pathways, Cell Reports, Volume 15, Issue 12, 2016, Pages 2809-2824, ISSN 2211-1247, https://doi.org/10.1016/j.celrep.2016.05.047.
- Azevedo S, Santos-Faria D, Leite Silva J, Ramos Rodrigues J, Sousa Neves J, Peixoto D, Tavares-Costa J, Alcino S, Afonso C, Teixeira F. Obesity, metabolic syndrome and other comorbidities in rheumatoid arthritis and psoriatic arthritis: influence on disease activity and quality of life. Acta Reumatol Port. 2019 Oct-Dec;44(4):322-324. English. PMID: 32281967.
- Moroni L, Farina N, Dagna L. Obesity and its role in the management of rheumatoid and psoriatic arthritis. Clin Rheumatol. 2020 Apr;39(4):1039-1047. doi: 10.1007/s10067-020-04963-2. Epub 2020 Feb 3. PMID: 32016655.
- Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity and inflammation: the linking mechanism and the complications. Arch Med Sci. 2017 Jun;13(4):851-863. doi: 10.5114/aoms.2016.58928. Epub 2016 Mar 31. PMID: 28721154; PMCID: PMC5507106.
- Dludla, P.V.; Nkambule, B.B.; Jack, B.; Mkandla, Z.; Mutize, T.; Silvestri, S.; Orlando, P.; Tiano, L.; Louw, J.; Mazibuko-Mbeje, S.E. Inflammation and Oxidative Stress in an Obese State and the Protective Effects of Gallic Acid. *Nutrients* 2019, *11*, 23. https://doi.org/10.3390/nu11010023
- Chelakkot, C., Ghim, J. & Ryu, S.H. Mechanisms regulating intestinal barrier integrity and its pathological implications. *Exp Mol Med* **50**, 1–9 (2018). https://doi.org/10.1038/s12276-018-0126-x

- Yang R, Chen Z, Cai J. Fecal microbiota transplantation: Emerging applications in autoimmune diseases. J Autoimmun. 2023 Apr 26:103038. doi: 10.1016/j.jaut.2023.103038. Epub ahead of print. PMID: 37117118.
- Smedslund G, Byfuglien MG, Olsen SU, Hagen KB. Effectiveness and safety of dietary interventions for rheumatoid arthritis: a systematic review of randomized controlled trials. J Am Diet Assoc. 2010 May;110(5):727-35. doi: 10.1016/j.jada.2010.02.010. PMID: 20430134.
- Haidmayer A, Bosch P, Lackner A, D'Orazio M, Fessler J, Stradner MH. Effects of Probiotic Strains on Disease Activity and Enteric Permeability in Psoriatic Arthritis-A Pilot Open-Label Study. Nutrients. 2020 Aug 5;12(8):2337. doi: 10.3390/nu12082337. PMID: 32764250; PMCID: PMC7468965.
- Tajik, N., Frech, M., Schulz, O. *et al.* Targeting zonulin and intestinal epithelial barrier function to prevent onset of arthritis. *Nat Commun* **11**, 1995 (2020). https://doi.org/10.1038/s41467-020-15831-7
- Dürholz K, Hofmann J, Iljazovic A, Häger J, Lucas S, Sarter K, Strowig T, Bang H, Rech J, Schett G, Zaiss MM. Dietary Short-Term Fiber Interventions in Arthritis Patients Increase Systemic SCFA Levels and Regulate Inflammation. Nutrients. 2020 Oct 20;12(10):3207. doi: 10.3390/nu12103207. PMID: 33092271; PMCID: PMC7589100.
- Colaco K, Lee KA, Akhtari S, Winer R, Welsh P, Sattar N, McInnes IB, Chandran V, Harvey P, Cook RJ, Gladman DD, Piguet V, Eder L. Association of Cardiac Biomarkers With Cardiovascular Outcomes in Patients With Psoriatic Arthritis and Psoriasis: A Longitudinal Cohort Study. Arthritis Rheumatol. 2022 Jul;74(7):1184-1192. doi: 10.1002/art.42079. Epub 2022 May 16. PMID: 35261189; PMCID: PMC9545279.
- Asquith M, Sternes PR, Costello ME, Karstens L, Diamond S, Martin TM, Li Z, Marshall MS, Spector TD, le Cao KA, Rosenbaum JT, Brown MA. HLA Alleles Associated With Risk of Ankylosing Spondylitis and Rheumatoid Arthritis Influence the Gut Microbiome. Arthritis Rheumatol. 2019 Oct;71(10):1642-1650. doi: 10.1002/art.40917. Epub 2019 Aug 12. PMID: 31038287.
- Olejniczak-Staruch I, Ciążyńska M, Sobolewska-Sztychny D, Narbutt J, Skibińska M, Lesiak A. Alterations of the Skin and Gut Microbiome in Psoriasis and Psoriatic Arthritis. Int J Mol Sci. 2021 Apr 13;22(8):3998. doi: 10.3390/ijms22083998. PMID: 33924414; PMCID: PMC8069836.
- Jacques, P.; Venken, K.; Van Beneden, K.; Hammad, H.; Seeuws, S.; Drennan, M.B. Invariant natural killer T cells are natural regulators of murine spondylarthritis. Arthritis. Rheum. 2010, 62, 988–999.

- Manasson J, Wallach DS, Guggino G, Stapylton M, Badri MH, Solomon G, Reddy SM, Coras R, Aksenov AA, Jones DR, Girija PV, Neimann AL, Heguy A, Segal LN, Dorrestein PC, Bonneau R, Guma M, Ciccia F, Ubeda C, Clemente JC, Scher JU. Interleukin-17 Inhibition in Spondyloarthritis Is Associated With Subclinical Gut Microbiome Perturbations and a Distinctive Interleukin-25-Driven Intestinal Inflammation. Arthritis Rheumatol. 2020 Apr;72(4):645-657. doi: 10.1002/art.41169. Epub 2020 Mar 12. PMID: 31729183; PMCID: PMC7113119.
- Paine A, Brookes PS, Bhattacharya S, Li D, De La Luz Garcia-Hernandez M, Tausk F, Ritchlin C. Dysregulation of Bile Acids, Lipids, and Nucleotides in Psoriatic Arthritis Revealed by Unbiased Profiling of Serum Metabolites. Arthritis Rheumatol. 2023 Jan;75(1):53-63. doi: 10.1002/art.42288. Epub 2022 Nov 25. PMID: 35818333; PMCID: PMC9797425.