Host genetic background disrupts the relationship between microbiota and gut mucosal tolerance leading to spondyloarthritis and ileitis after a dectin-1 trigger

**Spondyloarthritis**

- SpA
  - 1-3% population
  - Ankylosing spondylitis, psoriatic arthritis, reactive arthritis, enthesopathic arthritis, undiff.
  - Peripheral & axial joints, intestine, eyes, skin

- Genetic risk factors
  - HLA-B27 allele (90% AS)
  - Genes involved in IL-17 signaling: IL-23R, IL-12B, STAT3, CARD9, TYK2

- IL-23 and SpA
  - IL-23R risk allele increased signaling
  - IL-23 expression alone sufficient for SpA
  - Anti-IL-23 antibody (ustekinumab) blocks disease in human and mouse

**IL-23-dependent mouse model of human SpA**

- SKG mouse
  - Zap70 constitutive mutation (BALB/c)
  - Low TCR signal strength
  - Lymphopenia

- SKG disease phenotype
  - Beta-glucan curdlan-mediated (IYP)
  - Arthritis, spondylitis, enthesitis, uveitis, dactylitis, ileitis

**Spondyloarthritis**

- SpA
  - 1-3% population
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**SKG mouse model of SpA: disease initiation and progression**

- Day 0 – Treat with 3 mg curdlan i.p. (beta-glucan) Dectin-1 receptor
- Day 0  Day 7  Week 5  Week 8

**Arthritic disease (spondylitis, enthesitis, sacroiliac and ankle arthritis, plantar fasciitis)**

**Inflammatory bowel disease (ileitis)**

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References

- Stanislas Mondot, Daniel Aguirre De Cárcer, Philip Hansbro, A. The University of Queensland Diamantina Institute, Translational Research Institute, Brisbane, QLD
- Nothing to disclose
Microbes and SpA

Environmental trigger
- IL-17 immunity important pathogen control
- Infection (reactive arthritis)
- Microbiota implicated

Research Questions
- How do the microbiota and the host interact to induce IL-23?
- How does IL-23 promote disease?

Hypotheses
1) Host genetics influence microbiota composition
2) Microbiota (bacteria) affect disease severity in curdlan-treated SKG mice

Profile SKG microbiota

Acute inflammatory response is not dependent on the microbiota

Microbiota composition affects the severity of peripheral and axial arthritis, and ileitis in curdlan-treated SKG mice

However microbiota affect neutrophil IL-17A production in the peritoneal cavity

Co-housing SKG and BALB/c mice alters the genetic susceptibility to ileitis

GF = germ-free (no microbes)
SPF = specific pathogen-free (microbiota) altered Shaeder flora = 8 bacteria species

10% germ free SKG mice developed severe arthritis, no ileitis

Sequencing of microbiota d0 (untreated), d1, d3, d7, d14:
Do SKG and BALB/c microbiota normalize after 4 weeks co-housing? NO
Can curdlan induce microbiota shift? YES
Are there ‘pathogenic’ SKG strains colonizing diseased BALB/c? Are there ‘protective’ BALB/c strains colonizing protected SKG?
Genetic background and environmental trigger influence the microbiota composition

Impact of curdlan treatment on the microbiota following co-housing:
Dysbiosis!

Microbiota changes are associated with TLR4 signaling

Microbiota are associated with intestinal ER stress, IL-23 and MLN IL-17A production

Microbiota changes and intestinal stress are associated with reduced mucus-producing cells and tight junction protein expression

Conclusions and Implications

SKG microbiota
- ZAP70^W163C allele (reduced TCR signaling) alters microbiota composition of naïve SKG mice
- Curdlan triggers changes within the microbiota that are influenced by allele
- Microbiota composition affects disease severity

Clinical implication
- Genetic susceptibility may perturb microbiota of humans with SpA
- Microbial species predictive for disease development of at risk people
- Microbiota intervention prophylactic treatment
Genetics promote IL-23

Stressful interaction

IL-23

IL-17

β-glucan signaling

Dectin-1, neutrophils, γδ T cells, IL-17, NETs

Innate response through

Thyroid stromal cells

low TCR signaling immunodeficient

Inadequate microbe control or immune regulation

Genetics dictate microbiota

ATB treatment

Curdian primes IL-17A production in MLN of SKG mice

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Clostridia-related Gram-positive bacteria

Segmented Filamentous Bacteria – Th17??

Tight junctions intact in naïve and curdlan-treated SKG mice

SKG terminal ileum 15X EM

Day 0

Day 7
Acute inflammatory response is not dependent on the microbiota

Microbiota are necessary and sufficient for the development of peripheral and axial arthritis, and ileitis in curdlan-treated SKG mice

Curdlan triggers arthritis, and inflammatory bowel disease in SKG mice in an IL-23-dependent manner

SKG mouse model of human SpA

- SKG mouse description:
  - S. Sakaguchi (Nature 2003)
  - ZAP70W163C mutation
  - BALB/c genetic background
  - low TCR signal strength
  - lymphopenic, Th17 skewed T cells

- SKG disease phenotype:
  - Arthritis, spondylitis, enthesitis, uveitis, dactylitis, bone erosion and formation, ileitis
