Serum anti-microbial IgG analysis reveals differential host immune responses in OA patients compared to healthy controls

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INTRODUCTION: Previous studies have shown an association between gut dysbiosis and osteoarthritis (OA) risk in mice and humans. The mechanism underlying this association remains unclear. Previous research has also shown that microbiome-targeting IgG antibodies in blood can identify inflammation-inducing gut bacteria that translocate across the gut barrier to travel through the body. In the current study, we set out to determine whether serum anti-microbial IgG antibodies, reflective of translocated bacteria, were altered in OA patients compared to healthy controls.

METHODS: Serum samples were collected from 31 OA patients (20 knee, 1 hand, 4 erosive hand, 6 multi-joint OA) and from 27 matched healthy volunteers. A standardized fecal sample with a diverse gut bacterial community was prepared by combining stool samples from five healthy volunteers. Serum samples were incubated with the standardized stool samples, anti-IgG-PE microbeads were added, and IgG-positive and IgG-negative bacteria were separated using a magnetic bead approach. Bacterial DNA was extracted from each fraction, then DNA was amplified using PCR for 16s ribosomal RNA sequencing, which was performed on an iSeq 100 instrument (Illumina) to obtain 75-bp paired-end reads. The relative abundance of gut bacteria taxa in each sample type was quantified using QIIME2/Greengenes2 and the data collected analyzed to identify differences between patient and control groups using the prscores R-package.

RESULTS: We found no significant differences in overall IgG antibodies between OA patients and healthy controls. The mean presort IgG value was 0.141 ± 0.09 for OA patients and 0.170 ± 0.08 (P=0.4) for the control group. Five bacterial clades showed a significant difference in serum IgG antibody reactivity between OA patients and healthy controls (**Figure 1**): *Akkermarmansia muciniphila* (P=0.0236), *Anaerobacterium* (P=0.0138), *Eubacterium G* (P=0.0486), *Ruminococcaceae UBA134* (P=0.0017), *Staphylococcus* (P=0.0054), *and Megaspheraceae* (P=0.0486). OA patients were more likely to have IgG antibodies against *Ruminococcaceae UBA134* than the control group (OA: -0.12 ± 0.2; HC: -0.23 ± 0.1). The control group was more likely to have IgG antibodies against *Akkermarmansia muciniphila* (OA: -0.13 ± 0.3; HC: 0.16 ± 0.2), *Eubacterium G* (OA: 0.13 ± 0.2; HC: 0.23 ± 0.08), *Anaerobutyricum* (OA: -0.058 ± 0.2; HC: 0.15 ± 0.2), and *Staphylococcus* (OA: -0.052 ± 0.2; HC: 0.13 ± 0.2).

DISCUSSION: In the current study, we identified differences in species-specific gut microbiome IgG serum reactivity in OA patients compared to controls. did not find a difference in overall IgG positivity between OA and healthy control groups, although significant heterogeneity in the IgG positivity rate between samples was present. We did, however, note several differences in individual clades, including bacterial clades previously identified with OA and other forms of arthritis. These results suggest that the anti-microbiome host immune response may be both altered in OA patients and bacteria species-specific. Unlike single-timepoint gut microbiome composition analyses, this serum anti-microbiome IgG study provides a glimpse into long-term immune system exposure/memory to particular species which likely occurred through bacterial translocation across the gut barrier. Further research should confirm our findings, focus on identifying whether the host immune response to the microbiome extends to secreted immunoglobulin within the gut (anti-IgA), and analyze whether differences exist between different OA subtypes (e.g. knee, hand, erosive hand) in a larger cohort of samples.

SIGNIFICANCE/CLINICAL RELEVANCE: This study indicates that the systemic immune response to particular gut microbiome species is altered in OA patients and suggests there may be long-term differences in gut microbiome translocation during OA development.

IMAGES AND TABLES:

Figure 1: Anti-microbiome IgG antibodies in serum