OA-associated pain sensitivity is reduced in OA-protected MRL/MpJ mice, partially mediated by the gut microbiome, and transferable via microbiome transplantation

Gabriella Dyson[1,2], Montana Barrett[1,2], Nicholas Hanebutt[1,2], Aleksander Szymczak PhD[1], Cindy Miranda Brawner MS[1,2], Pratibha Dube[1,2], Elias Cherian[1], Austin Lopez[1], Padmaja Mehta-D'souza PhD[1,2], Matlock A. Jeffries MD[1,2,3]
[1]Oklahoma Medical Research Foundation, Oklahoma City, OK
[2]Oklahoma City VA Medical Center, Oklahoma City, OK
[3]University of Oklahoma Health Sciences Center, Oklahoma City, OK
Presenter: Gabby-dyson@omrf.org

Disclosures: Gabriella Dyson (N), Montana Barrett (N), Nicholas Hanebutt (N), Aleksander Szymczak (N), Cindy Miranda Brawner (N), Pratibha Dube (N), Austin Lopez (N), Padmaja Mehta-D'souza (N), Matlock A. Jeffries (Scientific advisor, Being, inc)

INTRODUCTION: MRL/MpJ (MRL) mice are protected from developing post-traumatic osteoarthritis (OA) histologic changes. We have previously shown the gut microbiome to play a key role in mediating this OA protection, wherein microbiome transplantation from MRL mice to B6 mice can prevent OA. The goal of the present study was to examine the effects of microbiome manipulation on OA-associated pain in MRL and wild-type C57BL/6 (B6) mice.

METHODS: The IACUC of the Oklahoma Medical Research Foundation approved this study. Young adult male B6 or MRL mice (11 weeks of age) underwent one-time microbiome transplantation via oral gavage of 200uL of diluted cecal contents from adult reciprocal-strain animals (n=6 MRL-into-B6, n=6 B6-into-MRL), or 200uL control solution (n=6 MRL, n=6 B6). One week later, unilateral destabilization of the medial meniscus (DMM) surgery was used to induce OA. Pain sensitivity thresholds were measured via small animal algometry of the operated and contralateral knees prior to intervention (10 weeks of age). Algometry data were collected every 4 weeks until euthanasia 12 weeks after DMM.

RESULTS: There were no differences at baseline in pain sensitivity, although there was a trend towards lower pain sensitivity in MRL animals at all timepoints (P=0.073 at baseline, P=0.069 at 4 weeks, P=0.033 at 8 weeks, P=0.16 at 12 weeks). At 4 weeks after DMM, MRL-into-B6 transplanted mice had substantially reduced pain sensitivity compared to B6 controls (P=0.0090), which was lost at later timepoints (P=0.17 at 8 weeks, P=0.23 at 12 weeks, **Figure 1**). B6-into-MRL transplantation did not alter pain sensitivity in MRL recipient mice at any timepoint. In the contralateral (unoperated) knee, we found MRL mice to have reduced pain sensitivity at all timepoints. MRL-into-B6 transplantation reduced pain sensitivity at 4 weeks (P=0.015) and 12 weeks (P=0.032). B6-into-MRL transplantation increased pain sensitivity at 4 weeks (P=0.012). Correlation of gut microbiome changes with pain sensitivity is ongoing.

DISCUSSION: Knee pain sensitivity is reduced in OA-protected MRL mice compared to wild-type B6 mice and is partially mediated by the gut microbiome, although the effects of a single timepoint microbiome manipulation are lost at timepoints beyond 4 weeks post-DMM. Limitations of this study include a small sample size and follow-up through moderate-stage disease (12 weeks). Future studies should investigate whether sustained changes in pain sensitivity could be seen with repeated microbiome manipulation, whether OA-associated behavioral changes are similarly mitigated with microbiome manipulation, and continue follow-up to end-stage disease (16 weeks and beyond).

SIGNIFICANCE/CLINICAL RELEVANCE: (1-2 sentences): This study indicates that the gut microbiome plays a role not only in OA histologic progression but also OA pain and suggests targets for future microbiome-based clinical interventions to reduce OA pain.

Figure 1: Pain sensitivity (withdrawal) thresholds by microbiome transpl. group