Objectives: To comprehensively investigate the intestinal mucosa cytokine production and DC, T and B cell responses to human gut microbiota associated with new-onset RA.

Methods: We utilized in vitro cultures of mucosal-like DCs (differentiated from bone marrow cells) and primary splenic DCs, as well as ex vivo cultures of healthy human intestinal biopsies, cultured in the presence of heat-killed fecal microbiota from either NORA or control donors. Furthermore, we performed studies in immunized mice carrying intestinal NORA microbiota, to study the effect on immune response during homeostasis and upon joint inflammation during collagen-induced arthritis (CIA) (RA).

Results: In 24h DC cultures, NORA fecal microbiota more potently induced the expression of co-stimulatory molecules CD40 and CD80, and IL-12 secretion by the NORA microbiome. Furthermore, in ex vivo cultures of human ileum biopsies, the production of IL-1 and IL-33, as well as IL-23/Th17 cytokines IL-23, IL-22, and GM-CSF, were significantly increased by NORA-derived microbiome. Interestingly, in the small intestine lamina propia (SI LP) of NORA-colonized mice, we observed enhanced Th17 polarization, increased innate GM-CSF expression and higher B cell CD40 and IgA levels during homeostasis. To study whether colonization with HC and NORA microbiota alters arthritis development, humanized mice and controls (mock, autologous, HC and NORA microbiota) were used in a CIA experiment. Macroscopic scoring of the arthritis severity at weekly intervals demonstrated that arthritis severity was significantly enhanced in NORA-colonized mice compared to HC-colonization and mock controls.

Conclusion: Our data reveal that NORA microbiota, in addition to the previously described Th17 differentiation, induce higher levels of GM-CSF and B cell IgA in LP and have increased potential to aggravate arthritis through the activation of TLR4.

References:

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