**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 humanized mice carrying intestinal NORA microbiota, to study the effect on immune response during homeostasis and upon joint inflammation during collagen-induced arthritis (CIA).

**Results:** In 24h DC cultures, NORA fecal microbiota more potently induced the expression of co-stimulatory molecules CD40 and CD80, and this enhanced DC maturation was partially mediated through TLR4 as demonstrated using the TLR4 antagonist TAK242. Interestingly, HC and NORA fecal microbiota differentially induced IL-12 and IL-6 production, with significantly enhanced IL-6 and reduced 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 propria (SILP) of NORA-colonized mice, we observed enhanced Th17 polarization, increased innate GM-CSF expression and higher B cell CD40 and IgA levels during NORA-derived microbiome. Interestingly, in the small intestine lamina propria (SILP) 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. Macrophage 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:**

**Disclosure of Interests:** Marije Koenders: None declared, Heath Evans-Marin: None declared, Joyce Aarts: None declared, Parvathy Girija: None declared, Rebecca Rogier: None declared, Sergei Korolov: None declared, Julia Manasson: None declared, Peter van der Kraan: None declared, Shaheh Abdollahi-Roodasaz: None declared, Jose Scher Consultant of: Novartis, Janssen, UCB, Marije Koenders: None declared, Heather Evans-

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**MIR-17-5P REDUCES INFLAMMATION AND BONE EROSIONS IN COLLAGEN INDUCED ARTHRITIS MICE AND DIRECTLY TARGETS THE JAK-STAT PATHWAY IN RHEUMATOID ARTHRITIS FIBROBLAST-LIKE SYNOVIOCYTES.

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**Background:** micro-RNAs (miR) are strong regulators of gene expression. Their involvement in RA key cytokines pathway regulation entities them as important players in RA pathophysiology. The miR-17-92 cluster has been widely studied in cancer as they regulate cell apoptosis.

**Objectives:** The aims of this study were to screen miR-17-92 cluster’s expression in different RA phenotypes (erosive and non erosive), further elucidate the mechanisms and direct targets involved in miR-17-5p anti-inflammatory role and to investigate miR-17-5p therapeutic effect in arthritis.

**Methods:** A miR array was performed in synovial tissue from naive erosive and non-erosive RA patients. Intra-articular delivery of miR-17-5p lipoplex was performed in collagen induced arthritis model in mice. Clinical, histological and structural effects were studied over the course of arthritis. In depth studies of miR-17 mechanisms of action were performed in primary RA-FLS isolated from RA synovial tissue.

**Results:** Among others, miR-17-5p expression was reduced in erosive RA, miR-17 transfection in arthritic paws significantly reduced clinical inflammation. Moreover, synovial B cells, T cells, macrophages and polymuclear neutrophils infiltrates were significantly reduced. Structural damage was also decreased as shown by a reduction in the number of osteoclasts and erosion score by CT analysis. Pro-inflammatory cytokines of the IL-6 family, STAT3 target genes and IL-1β expression were also significantly reduced, but not TNF-α. miR17 directly targeted the 3’‐untranslated region of STAT3 and JAK1, STAT3 and JAK1 mRNA and protein expression were reduced in RA-FLS following miR-17 transfection. STAT3 and JAK1 mRNA and activation of STAT3 as assessed by immunohistochemistry were also reduced in injected paws.

**Conclusion:** We demonstrate an anti-inflammatory and anti-erosive role of miR-17 in vivo. This effect involves the suppression of the IL-6 family autocrine amplifying loop through the direct targeting of JAK1 and STAT3 as shown in RA-FLS.