for targeted and therapeutic manipulation of the microbiota in chronic inflammatory diseases.

Methods We have developed high-resolution microbiota flow cytometry which allows us to analyze the microbiota on a single cell level. This provides a non-invasive, fast and efficient diagnostic tool to visualize dramatic changes of microbiota composition in inflammatory diseases, fast and efficiently, and isolate distinct bacteria for functional and molecular analyses.

Results We have identified bacteria belonging to the genus *Anaeroplasm*, which enhances the levels of mucosal IgA. Adoptive transfer of *Anaeroplasm* increases the numbers of IgA+ germinal center B cells in the Peyer's patches and of IgA-secreting plasma cells in the lamina propria of the small intestine leading to significantly enhanced mucosal IgA levels. *Anaeroplasm* controls IgA expression presumably its ability to induce expression of the regulatory cytokine TGF- β in T cells, as we show here.

Conclusions The anti-inflammatory properties of *Anaeroplasm* to induce the anti-inflammatory cytokine TGF- β , thereby also strengthening the intestinal barrier by enhancing mucosal IgA, qualify *Anaeroplasm* as potent probiotic for the prevention and treatment of chronic inflammation.

Disclosure of Interest None declared.

P105

IDENTIFICATION OF RARE CODING VARIANTS IN IL-1-RELATED PATHWAYS IN PATIENTS WITH ADULT-ONSET STILL'S DISEASE

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Career situation of first and presenting author Assistant.

Introduction Adult-onset Still's disease (AOSD) is a rare auto-inflammatory disease characterized by fever, arthritis, and multi-organ involvement. Inflammation in AOSD is mediated by interleukin (IL)-1 β , as confirmed by the clinical efficacy of selective blockers. The genetic predisposition to this IL-1-driven inflammation remains nevertheless elusive. Previous studies failed to identify associations between polymorphisms in the IL-1 genes and AOSD, thus pointing at more complex genetic mechanisms. These cannot be investigated with traditional techniques for genetic partitioning, such as GWAS, which only assess common variants and polymorphisms. Studies focusing on highly penetrant rare variants or different types of mutations (i.e. small copy-number variations; insertions/deletions) are warranted.

Objectives We hypothesized that genetically determined changes in IL-1-related pathways resulting in excessive IL-1 β activity lead to the development of autoinflammation in AOSD. Scope of this study was to unravel the combined mutational variation of a network of IL-1-related receptors, pathways, counter-regulators, and cellular processes possibly involved in the pathogenesis of IL-1-mediated inflammation.

Methods We collected clinical and genetic data from a large cohort of 76 AOSD patients and developed an innovative platform based on molecular inversion probes technology, which enables highly multiplexed targeted-resequencing of the coding sequence of 48 genes related to the IL-1-pathway, and allows studying rare and common variants in one assay. We have also screened 500 healthy controls, and 1000s of samples with other disorders using the same assay.

Results We identified rare and unique (i.e. private variants) in the IL-1 pathway in several individuals with AOSD. Whether any of these are involved in a strong predisposition to AOSD is currently followed-up. Rare genetic variants have been identified in six IL-1-pathway 'clusters':

1. Inflammasomes;
2. IL-1 pathway;
3. IL-1 family;
4. IL-18 pathway;
5. Autophagy;
6. ROS production.

Conclusions Unraveling the genetic bases of inflammation in AOSD deepens our understanding of the human innate immunome. This study platform may now serve for the genetic analysis of other IL-1-mediated conditions (i.e. gout and other autoinflammatory diseases), whose genetic predisposition remains elusive. Equally important, the identification of pathways amenable to targeting with small molecules or biologics may translate into remarkable clinical implications.

Disclosure of Interest None declared.

P106/O25

DNA METHYLATION IN LYMPHOCYTE SUBSETS AS A MEDIATOR OF GENETIC RISK IN EARLY RHEUMATOID ARTHRITIS

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Career situation of first and presenting author Student for a master or a PhD.

Introduction Genome-wide association studies (GWAS) have identified over 100 RA-associated risk loci, whose enrichment for lymphocyte-specific enhancer elements is consistent with a regulatory function of many causal variants in these cells. Epigenetic modifications have also been strongly implicated in RA pathogenesis.

Objectives To investigate the role of DNA methylation as a mediator of RA genetic risk.

Methods CD4+ T lymphocyte-specific DNA and RNA were extracted from freshly isolated blood of 43 RA and 60 disease control patients, along with equivalent material from B-lymphocytes of 46 RA and 73 controls. Comparator groups were drug-naïve and matched for age, sex, and acute phase response. Genotyping, gene expression and methylation

profiling was carried out using Illumina chip array technology. After mapping genome-wide methylation quantitative trait loci (mQTLs) in *cis* (<1 Mb), we focused on known RA risk loci, integrating paired normalised gene expression measurements for transcripts within 500 kb of index CpGs. We also sought *trans* mQTLs, highlighting RA-specific effects.

Results CD4+ T lymphocyte *cis*-mQTLs co-localised with 30 independent ($r^2 < 0.8$) RA-associated SNPs, whilst in B lymphocytes such mQTL effects were present at 31 RA SNPs. 80% of these variants functioned as *cis*-mQTLs in both cell types. CpG sites subject to *cis* effects at risk loci were depleted in regions associated with cell type-specific repressed chromatin marks, with enrichment at enhancer regions and those flanking transcription start sites, suggesting active roles in transcriptional regulation. Linear regression identified regulatory effects of these CpG sites on gene expression, and causal inference testing highlighted genes for which risk SNPs most likely modulate gene expression via CpG methylation. Such effects, robust to false discovery rate, were particularly prevalent in CD4+ T lymphocytes, for example implicating *ANKRD55*, *ORMDL3*, and *FCRL3* as causal genes in this cell type. Our analysis of mQTLs acting in *trans* identified inter-chromosomal SNP-CpG associations, also revealing instances of differential effect size in RA patients and controls.

Conclusions Here we highlight an important mechanism by which genetic variants may contribute to altered lymphocyte phenotype, and demonstrate the utility of DNA methylation profiling as a tool for the prioritization of candidate genes following GWAS studies in RA. The functional roles of highlighted genes in CD4+ T cells during RA pathogenesis await clarification.

Disclosure of Interest None declared.

P107

POLYMORPHISMS IN SLC2A9 AND SLC22A12 GENES ARE RELATED TO HYPERURICEMIA, GOUT AND ALSO TO HYPOURICEMIA

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Career situation of first and presenting author Student for a master or a PhD.

Introduction Serum uric acid concentration is significantly influenced by urate transporters, such as ABCG2 (encoded by *ABCG2* gene), GLUT9 (*SLC2A9* gene) and URAT1 (*SLC22A12* gene). The main function of ABCG2 is uric acid secretion, whereas GLUT9 and URAT1 also ensure reabsorption. Pathogenic allelic variants in *SLC2A9* and *SLC22A12* are not only associated with hyperuricemia and gout, but they also lead to rare hereditary renal hypouricemia (type 1 – OMIM #220150 or type 2 – OMIM # 612076).

Objectives Previously, we analyzed *ABCG2* gene and detected non-synonymous variants that lead to hyperuricemia and early onset of the gout.¹ The aim of this study was to find a possible correlation between variants in *SLC2A9* and *SLC22A12* and hypouricemia, hyperuricemia and gout.²

Methods We recruited a cohort of 232 individuals with primary gout and hyperuricemia. We examined coding regions of

SLC2A9 (13 exons) and *SLC22A12* (10 exons) by Sanger sequencing. We also analyzed *SLC2A9* and *SLC22A12* in five patients with suspect hypouricemia.

Results In the cohort of 232 individuals, we detected five synonymous variants, 18 intron variants and seven missense variants in *SLC2A9*: A17T, G25R, T275M, D281H, V282I, R294H, and P350L. In *SLC22A12* gene, we found six synonymous variants and seven intron variants.

We detected several pathogenic variants in patients with suspect hypouricemia. Intronic variant c.1419+1G>A in *SLC2A9* most likely affects the splicing. In *SLC22A12*, we found rare pathogenic variants T467M and L415_G417del. These variants have according to our previous study high frequency in the Czech and Slovak Roma population.³

Conclusions The uric acid level is determined by a complex mechanism that is not yet fully understood. Disorders of urate transporters can not only lead to hyperuricemia, but in rare cases also to hypouricemia.

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P108/028

FATTY ACID OXIDATION CAN DRIVE HUMAN MONOCYTE DERIVED CCL20 IN THE RA SYNOVIAL ENVIRONMENT

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Career situation of first and presenting author Post-doctoral fellow.

Introduction Metabolic pathways are considered to have a governing role in inflammatory cascades in myeloid cells. This is particularly evident in murine macrophages where glycolysis and fatty acid oxidation (FAO) have been implicated in inflammatory cascades and immune regulation respectively.¹ However, investigation of intracellular metabolism of human monocytes in the context of the hypoxic and inflammatory RA synovium is lacking.

Objectives To mimic the hypoxic RA environment *in vitro* and metabolically profile human monocytes. Determine if altered metabolic pathways have a functional impact on monocytes under disease-relevant conditions.

Methods Human monocytes were isolated from buffy coats and were exposed to hypoxia *in vitro*. Metabolic profiling of monocytes was carried out by LC-MS metabolomics. Inflammatory mediator release after LPS or RA-synovial fluid (RA-