**Spondyloarthropathy - aetiology, pathogenesis and animal models**

**POS0422**

**METABOLIC FINGERPRINT TO DISCRIMINATE REMISSION FROM ACTIVE DISEASE AND HEALTHY CONTROLS IN PSORIATIC ARTHRITIS**

**Keywords:** Psoriatic arthritis, Biomarkers, Remission

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**Background:** Among the unmet needs in psoriatic arthritis (PsA), the discovery of molecular players and biomarkers of disease activity or clinical remission achievement, remains unsolved. Metabolomics is a valuable technology in identifying biomarkers, by the study of a set of small molecules produced by the catabolism or anabolism of an organism in response to physiological or pathological states, allowing to better understand the disease-related variations downstream of the genome and proteome.

**Objectives:** In this pilot study, we have compared the serum metabolomics profiles of patients with psoriatic arthritis with active or clinically inactive disease state compared with healthy controls, using Nuclear Magnetic Resonance Spectroscopy (1H-NMR).

**Methods:** From a cohort of 300 PsA patients according to CASPAR criteria, we selected 30 PsA with active disease state by DAPSA >14 score (no bDMARDs ongoing) (A), 38 patients (peripheral arthritis subset) with >1-year remission by anti-TNFα assessed by DAPSA ≤ 4 (B) and 32 healthy controls (C) matching for mean age and gender ratio. The sera metabolomics profile of 100 subjects was analyzed with a Varian UNITY INOVA 500 MHz NMR spectrometer, combined with Multivariate statistical Analysis (MVA), Principal Component Analysis (PCA) and Orthogonal Partial Least-Squares Discriminant Analysis (OPLS-DA) were applied. The model’s goodness was evaluated using a permutation test (Q2 intercept value <0.005).

**Results:** The represented OPLS-DA models (Figure 1) exhibited a clear separation between subjects with active disease (red dots) and healthy controls (green dots), and patients with active disease or clinical remission state (blue dots), indicating significant differences in the serum metabolomics profile between all compared conditions. Interestingly, the OPLS-DA model shows how the PsA patients in the remission state have a profile which does not completely overlap with healthy subjects. The validity of the OPLS-DA models was evaluated through a permutation test using 500 times (Table 1) and indicate the great statistical validity of the OPLS-DA reported models.

**Conclusion:** The metabolic profile of PsA patients with different disease state and healthy subjects reveal a high grade of dissimilarity between all compared conditions: remarkably, the metabolic profile of patients with the drug-induced clinical remission appears still different from a healthy condition, perhaps reflecting molecular modifications induced by the great response to TNFα inhibition sustaining the clinical remission of PsA disease. Supplementary analysis of single-spectra is ongoing to obtain a list of metabolites differentially expressed in all conditions, and on this field further explorations are needed to validate metabolite-modulation biomarkers that can accurately and reliably measure PsA disease activity or remission achievement, as well as to identify the metabolic fingerprint of anti-TNFα-treatment success.

**Table 1. Parameters for OPLS-DA models**

<table>
<thead>
<tr>
<th>OPLS-DA models</th>
<th>Permutation (500 times)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>active PsA patients vs healthy controls</td>
<td>Components* R2Xcum2 R2Ycum1 G2cum2 R2 intercept G2 intercept</td>
</tr>
<tr>
<td>1P+1O</td>
<td>0.406 0.665 0.517 0.330 -0.336</td>
</tr>
<tr>
<td>active PsA patients vs remission PsA patients vs healthy controls</td>
<td>0.481 0.824 0.504 0.461 -0.424</td>
</tr>
</tbody>
</table>

*The number of Predictive and Orthogonal components used to create the statistical models. R2X and R2Y indicated the cumulative explained fraction of the variation of the X block and Y block for the extracted components. G2 cum values indicated cumulative predicted fraction of the variation of the Y block for the extracted components. An G2 intercept value less than 0.005 are indicative of a valid model.

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**Disclosure of Interests:** None Declared.

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**POS0423**

**PLASMA METABOLIC PROFILES OF PATIENTS WITH ACTIVE PERIPHERAL PSORIATIC ARTHRITIS CAN DIFFERENTIATE TREATMENT RESPONDERS FROM FAILURES: EXPLORATORY FINDINGS FROM THE FLORA TRIAL**

**Keywords:** -omics, Psoriatic arthritis, Gastrointestinal tract

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**Background:** Metabolite profiling of biofluids has an emergent role in exploring the contribution of host-microbiome interactions to the treatment response of immune-mediated arthritis.[1]

**Objectives:** As part of the FLORA trial (exploring the impact of gut microbiome manipulation upon response to methotrexate (MTX)),[2] we investigated plasma metabolic profiles of adults with psoriatic arthritis (PsA) and whether they correlated with the primary trial outcome, which was clinical response to MTX (responder vs failure) following one faecal microbiota transplant (FMT) or sham transplant.

**Methods:** Thirty-one PsA patients with active peripheral disease, despite initial 3 months of steady-state MTX, were included in the 26-week, double-blind, parallel-group, 1:1 randomised, sham-controlled, superiority trial (FLORA trial; NCT03058900).[2] Patients were randomly allocated to receive either one gastrointestinal-guided FMT (n = 15) or sham transplant (n = 16). Each FMT product encompassed 50 g of processed faeces obtained from one of four healthy, thoroughly screened donors. Patients continued MTX throughout the trial. The primary trial endpoint was the proportion of treatment failures through 26 weeks, defined as need for treatment escalation (in most cases instigation of TNF inhibitors) due to insufficient improvement of disease activity or disease worsening.[2] Li-Hep plasma samples were collected at baseline, week 4, 12, and 26. The metabolic profiles were measured using 1H Nuclear Magnetic Resonance (NMR). We used a supervised multivariate orthogonal partial least-squares-discriminant analysis (OLPS-DA) to model metabolic differences among groups.

**Results:** Twenty women and eleven men with a mean age of 50.7 years (SD = 13.6) and a mean swollen joint count of 7.1 (SD = 2.8) were included in the trial.[2] We were able to annotate 40 plasma metabolites in the baseline samples. No differences in baseline plasma profiles were observed between patients allocated to FMT and sham (OLPS-DA model; Q2 = -0.452, p = 1). However, the OPLS-DA analysis revealed a significant model for treatment responders (n = 19) vs failures (n = 12) among all patients, Figure 1. Correlations between metabolites and the primary trial outcome with a correlation coefficient (r) ≥0.50 are presented in Table 1. When patients were stratified for intervention type, the models continued to show significant separation (FMT arm: Q2 = 0.383, p < 0.0001; sham arm: Q2 = 0.260, p = 0.002). In both the FMT and the sham models, glucose (r = 0.67 and r = 0.63) correlated positively with treatment failure.

**Figure 1.** OPLS-DA scores plots of 1H NMR spectra of sera samples. Red dots: (A) active PsA patients; blue dots: (B) remission PsA patients; green dots: (C) healthy controls.

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while lysine ($r = -0.83$ and $r = -0.65$) and phenylacetate ($r = -0.66$ and $r = -0.51$) correlated with successful treatment response.

**Figure 1.** OPLS-DA model that significantly separates treatment responders ($n = 19$) from failures ($n = 12$) based on their plasma metabolomic profiles. Plot includes $^1$H-NMR plasma profile for all patients at all timepoints.

**Table 1.** Plasma metabolites associated with successful treatment response (green) vs failure (blue) in the Figure 1 model.

<table>
<thead>
<tr>
<th>Plasma metabolite</th>
<th>Correlation coefficient</th>
<th>Positive correlation with</th>
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<tbody>
<tr>
<td>Lysine</td>
<td>-0.61</td>
<td>Responder</td>
</tr>
<tr>
<td>Valine</td>
<td>-0.54</td>
<td>Responder</td>
</tr>
<tr>
<td>Serine</td>
<td>-0.50</td>
<td>Responder</td>
</tr>
<tr>
<td>Alanine</td>
<td>0.82</td>
<td>Failure</td>
</tr>
<tr>
<td>N-acetylglutamine</td>
<td>0.81</td>
<td>Failure</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.80</td>
<td>Failure</td>
</tr>
<tr>
<td>Lipid CHICO</td>
<td>0.80</td>
<td>Failure</td>
</tr>
<tr>
<td>Citrate</td>
<td>0.78</td>
<td>Failure</td>
</tr>
</tbody>
</table>

**Conclusion:** In the FLORA trial, plasma metabolomic profiles of patients with active, peripheral PsA significantly discriminated between treatment responders and failures. This discriminatory power was the case for the entire trial population as well as for each of the two treatment arms (FMT vs sham).

**REFERENCES:**


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**Disclosure of Interests:** None Declared.

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**POS0425**

**SINGLE-CELL RNA SEQUENCING OF SYNOVIAL TISSUE-DERIVED MYELOID CELLS IN PSORIATIC ARTHRITIS PATIENTS ACROSS DISEASE PHASES**

**Keywords:** Synovium, Biomarkers, Innate immunity

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**Background:** Single cell technologies (scRNAseq) are increasingly applied in rheumatology to identify key cellular phenotypes that drive disease pathogenesis, enabling to deconvolute cellular heterogeneity within tissues.

**Objectives:** To investigate ST heterogeneity in terms of myeloid cells enrichment and distribution across different disease phases on ST samples obtained from US-guided biopsies in a bio-samples dataset of patients with Psoriatic Arthritis (PsA).

**Methods:** 17 patients fulfilling the CASPAR criteria for PsA underwent US-guided ST biopsy and were included. At baseline, patients were categorized based on their disease phase: n=4 naïve to D-MARDs; n=3 resistant to c-D-MARDs; n=5 resistant to b-D-MARDs; n=2 difficult to treat and n=3 in sustained clinical and US remission or in low disease activity (LDA) state. All ST specimens were processed for phenotyping and sorting. Alive cells were sorted and loaded onto a Chromium Controller (10x Genomics) for single-cell partitioning, followed by library preparation according to the Chromium Next GEM Single Cell 3’ Reagents Kits v3.1 (Dual Index) protocol. Single-cell libraries were sequenced on the Illumina HiSeq 4000 system to a minimum depth of 20,000 reads per cell.

**Results:** After standard data processing and quality control procedures, we obtained transcriptomic profiles for 16701 synovial tissue-derived cells. For analysis of ST myeloid compartment only, 10194 cells were computationally isolated with the same subset function from other cell types based on expression of CD14, MARCO,LYZ,CD11b and CD64. We identified 10 different myeloid subclusters from the scRNA-seq profiles using SCTransform integration: 2 clusters of lining layer and 8 sublining layer macrophage named after main differentially expressed genes (adjusted P < 0.05 by Bonferroni correction and multiple test correction, multiplied by number of tests) and according to the nomenclature established in Alvernoi et al. 2020. Each cell type group is present across all disease conditions but differences in relative proportions were detected. Specifically, ST of patients with active PsA resistant to pharmacological treatment was significantly enriched in sublining MerTKnegSPP1pos macrophages. In addition, we observed pro-inflammatory changes in lining layer TREM2pos STMs as compared to patients who achieved Remission/LDA status (<0.001 for both).

**Conclusion:** MerTKnegSPP1pos STM macrophage may contribute to synovial pathology of PsA resistant to pharmacological treatment.