Methods: 696 samples were identified from a previous genetic study in obesity where each patient was systematically examined with BMI and other related anthropometric measures were recorded. No patients had psoriasis, inflammatory arthritis or any extra-articular manifestations of spondyloarthritis. Samples were genotyped using a PsA-weighted single nucleotide polymorphism (SNP) panel, representing genetic variants associated with PsA. The cohort consisted of 73% female with an average age of 49 years $\pm$ 15. The average BMI of the group was 35 $\pm$ 8 kg/m², ranging from 17 to 67 kg/m². The PsA SNP panel consists of 42 SNPs associated with PsA including *IL23R*, *5q31*, *PTPN22*, *TNFAIP3*, *HLA-C*, *TNFRSF9*, *LCE3A*, *ADAMTS9-MAG1*, *HLA-B*, *IL13*, *MICA*, *IL12B*, *ZNF8816A*, *TRAF3IP2*, *KIR2DS2*, *FBXL19*, *REL*, *IL23R*, *IL23A*, *TNIP1*, and *TYK2*. DNA (10ng/ μ L) was used to prepare a PCR, followed by SAP, and extension reaction with Agena iPLEX Pro kit using Agena MassARRAY. Quantitative trait analysis was performed to obtain the association between BMI and genotype of the 42 SNPs using a linear regression model. Bonferroni correction was used to adjust for multiple comparisons. The factors of age, gender, smoking and height also have been adjusted in the analysis (Table 1).

Table 1. Regression analysis between BMI and 2 significant SNPs

SNP	CHR	Allele 1	Allele 2	BETA	SE	T	P (Genotype Only)	P (adjusted with factors)*
rs3131382	6	T	C	2.227	0.7207	3.17	0.001596	5.40E-05
rs10782001	16	G	A	1.584	0.4347	3.644	0.00029	0.0007524
Genotypes of FBXL19 and HLA-B*39:05 SNPs with mean BMI								
SNP	rs3131382					rs10782001		
Genotypes	TT	TC	CC	GG	GA	AA		
Sample Counts	6	99	575	75	324	246		
Genotype Frequency	0.0088	0.15	0.84	0.11	0.50	0.38		
Mean BMI	47.17	36.73	35.46	37.29	36.36	34.43		
SD	16.07	6.64	7.12	7.68	7.40	6.83		

*Adjusted for age, sex, height, and smoking

Results: Linear regression analysis with and without clinical factors for the two significant SNPs are presented in Table 1. Genotypes of two SNPs (rs10782001 and rs3131382) showed a difference with BMI (Table 1). The rs10782001 variant is within *FBXL19* and the average BMI in the presence of GG genotype was 37.2 vs 34.3 for the AA genotype ($p=0.0007$). The rs3131382 variant is within *HLA-B*39:05* and the average BMI with TT genotype was 47.1 vs 35.4 for the CC genotype ($p=0.00005$). Both SNPs maintained significance after correction for multiple testing ($p<0.001$).

Conclusion: Homozygotes for the minor allele of SNPs within *HLA-B*39* and *FBXL19* have shown to have an increased BMI, suggesting a potential genetic link between these genes and PsA and obesity. Interestingly, it has been recently noted that miR-26 suppresses adipocyte progenitor differentiation and fat production by targeting *FBXL19*, leading to possible biologic possibility regarding the link between PsA-weighted genetic variants and obesity⁴.

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miRNAs Deregulated in Response to IL17A Inhibitors in Psoriatic Arthritis Regulate Gene Products in Rho-GTPase Pathways

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Background: Using transcriptomic data at initiation of therapy, we recently identified differentially expressed genes (DEGs) that separated IL-17Ai response from non-response¹. Integration of cell-type-specific DEGs with protein-protein interactions (PPIs) and further comprehensive pathway enrichment analysis revealed Rho GTPase signaling pathway exhibited a strong signal specific to IL-17Ai response and particularly the genes, *RAC1* and *ROCKs*.

Objectives: To characterize microRNA (miR) profiles among IL-17Ai responders and non-responders, as it relates to RHO GTPase pathway.

Methods: We interrogated 20 psoriatic arthritis (PsA) patients initiating IL-17Ai. Patients achieving at least low disease activity according to the Disease Activity Index for PsA (DAPSA) at three months were classified as responders. There were seven responders (35%) and thirteen non-responders (65%) in the IL-17Ai group, with biologic treatment naïve (bio-naïve) and previously-exposed (bio-exposed) patients exhibiting a 50% (4/8) and a 25% (3/12) response rate, respectively. For the miR analysis, CD4 positive T cells were isolated from peripheral blood mononuclear cells using Dynabeads™ CD4 beads (ThermoFisher). Total RNA was extracted from the CD4⁺ T cells using Lexogen's Split RNA Extraction Kit (D-Mark Biosciences). Libraries were prepared from 200ng total RNA with the NEXTFLEX Small RNA-Seq Kit v3 with UDIs (Bioo Scientific) and sequenced on the Illumina NovaSeq 6000. Raw sequencing fastq data assessed the quality using FastQC. The miRDeep2 was used to trim the adapter, align and quantify human mature miRs from miRbase (Release 22). The abundance of miRs was converted to read counts per million, normalized and limma R package was used to identify pre- and post-differentially expressed miRs.

Results: We obtained 2,889 miRs. After removing miRs with low reads in >90% of samples, 1902 high quality miRs remained for further analysis. Using miRDI v4.1 we identified gene targets for differential miRs, and focused on recently identified DEGs related to RHO GTPase pathway. The miRs on the left of the figure 1 are those deregulated in pre-treatment, and the miRs on the right of the figure 1

Figure 1.

show the post-treatment deregulated miRs. hsa-miR-3691-5p and hsa-miR-3161 represent the miRs that were deregulated in both conditions. The red highlighted nodes represent the most connected miRs and genes; thus, representing miRs that are the most RHO-pathway centric regulators (hsa-miR-495-3p, 16-5p, 129-5p, 520h, 520g-3p), and genes representing the most strongly regulated RHO-pathway gene products (*ROCK1*, *RHOQ*, *PFN2*, *TAOK1*, *DYNC1L12*, *MAPRE1*, *PAFAH1B1*, *ARHGAP5*, *MAPK1*, *CALM1*, *DIAPH2*, *PKN2*, *ITSN1*).

Conclusion: Pre- and post-treatment differential miRs related to IL-17Ai response regulate multiple genes from RHO GTPase pathway.

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POS0407

PROTEOMICS ANALYSIS COMPARING THE MODE OF ACTION OF UPADACITINIB BETWEEN NON-BIOLOGIC-DMARD-IR AND BIOLOGIC-DMARD-IR PsA PATIENTS IDENTIFIES DISTINCT PATHOGENIC PATHWAYS IN THE SELECT-PsA 1 AND SELECT-PsA 2 PHASE 3 STUDIES

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Background: Treatment of non-biologic-DMARD-IR¹ (DMARD-IR) and biologic-DMARD-IR² (bio-IR) PsA patients with upadacitinib (UPA) at 15 mg QD, an oral JAK1 selective inhibitor, resulted in significant improvement in signs and symptoms compared to placebo.

Objectives: Using a pre-defined set of inflammation-related plasma protein biomarkers (pBM), to explore immunological pathway modulation by UPA 15 mg QD in PsA patients with active disease despite treatment with non-biologic or biologic DMARDs in the context of clinical response vs. non-response to treatment.

Methods: Patients from the SELECT-PsA 1 (DMARD-IR) and the SELECT-PsA 2 (bio-IR) studies were randomly selected (PBO, n=100; UPA 15 mg QD, n=100 for each study). The levels of 92 inflammation related protein biomarkers (pBM) were analyzed using a multiplexed Proximity Extension Assay platform in plasma samples collected at baseline, week 2, and 12; change from baseline in protein levels was expressed as Log₂ Fold Change; a Repeated Measure Mixed Linear Model was used to identify pBM modulated by UPA compared to Baseline, and those differentially modulated between responders (R) and non-responders (NR) according to ACR50, PASDAS Minimal Disease Activity, and PASI75 at week 12. Correlation of disease activity measures with relative levels of pBM were derived using Pearson's correlation; PASI score was transformed as Log₁₀ (x+1) prior to the analysis. Functional pathway prediction was performed in silico with a commercial distributed software.

Results: At baseline, the relative levels of 37 pBM correlated with at least one baseline disease activity measure, with a marked positive correlation of IL6 with musculoskeletal end points (PASDAS and DAS28CRP), and a strong positive correlation of IL20, IL17A, IL17C, and TGFA with baseline PASI.

At the single pBM-level, treatment with UPA 15 mg QD resulted in a down modulation of pBM associated with T cells, myeloid cells, and IFN-, IL6-, and TNF-related pathways in both DMARD-IR and bio-IR PsA patients. Overall effects of UPA on single pBMs were broadly similar between DMARD-IR and bio-IR patients. However, analysis of pBMs differentially modulated by UPA in R vs NR indicated that favorable clinical response (achievement of ACR50, PASDAS MDA, and PASI75) in DMARD-IR patients was associated with the down modulation of pBMs predicted to be linked to IFN, IL10, IL17, IL22, and IL27 pathways; while favorable clinical response in bio-IR patients was associated with the down modulation of multiple pBM predicted to be linked to the IL17, IL23, and IL1 pathways.

Conclusion: UPA effects in both DMARD-IR and bio-IR PsA patients likely stem from the direct and indirect inhibition of multiple biological pathways belonging to the adaptive and innate immune systems. Responder/Non-Responder analysis suggests a possible shift from a TH1 biased biology in DMARD-IR PsA patients to a more TH17 biased biology in bio-IR PsA patients. This apparent change in the disease biology of PsA patients after inadequate response to prior therapy could be attributed to the actual alteration of the disease biology, treatment outcome-based patient selection, or both. Considering the clinical efficacy of UPA in both DMARD-IR and bio-IR PsA patients, this observation highlights the importance of targeting multiple pathways with drugs such as UPA for the treatment of a broad range of PsA patients.

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POS0408

INVESTIGATING THE ANTI-INFLAMMATORY POTENTIAL OF A NOVEL MK2 INHIBITOR IN A VITRO MODEL OF ENTHESITIS

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Background: Enthesitis or inflammation of tendon/ligament anchorage points is the cardinal lesion in spondyloarthritis (SpA). Through the use of cytokine targeting biologics and also murine models, several key mediators have been shown to have a role in enthesitis, such as IL-23/17 axis and TNF¹. We have previously shown that the human enthesis contains myeloid cells capable of IL-23 and TNF production and range of T-cells capable of IL-17A/F secretion^{2,3}. Attempted inhibition of p38 MAPK for inflammatory disease in the past has yielded toxicity issues. The MAPK-associated protein kinase 2 (MK2) is situated downstream of p38 MAPK, relaying the phosphorylation signal to the nucleus, and is thus a promising target.

Objectives: To determine if a novel MK2 inhibitor (MK2i) could suppress innate and adaptive immune responses in an in vitro human enthesis model.

Methods: Normal spinous process enthesis was obtained from patients undergoing spinal decompression or surgery for scoliosis correction. Following enzymatic digestion, enthesal cells (n=5) were harvested and stimulated either with LPS/IFNγ (Enthesal myeloid cell activator) or anti-CD3 (Enthesal T-cell activator) with and without MK2i (1, 0.1 and 0.01 μM) for 24 hr. Supernatant was harvested and protein detected using multiplexing for panels relating to inflammation (IL-1β, IFN-α2, IFN-γ, TNF, CCL2, IL-6, IL-8, IL-10, IL-12p70, IL-17A, IL-18, IL-23, and IL-33) or T-cell activation (IL-2, IL-4, IL-5, IL-6, IL-9, IL-10, IL-13, IL-17A, IL-17F, IL-22, IFN-γ and TNF).

Results: Following LPS/IFNγ stimulation of enthesal cells, 1 μM MK2i significantly attenuated secretion of TNF, IFNα, IL-6, IL-10, IL-8 and CCL2.