Psoriatic arthritis (PsA) is a multifaceted inflammatory disease that affects approximately 0.25% of the global population. A range of disease modifying drugs has been used to treat PsA including Abatacept. Unfortunately, not all PsA patients respond to Abatacept treatment and some patients may be intolerant, thus there is an urgent need for the improved selection of patients who are likely to respond Abatacept treatment.

Objectives: This pilot project seeks to demonstrate the potential with which MS based proteomics strategies might be used to discover proteins that may discriminate responders from non-responders to treatment with Abatacept. Using syrovial samples collected at baseline and a label-free nLC-MS/MS strategy, candidate proteins were identified. These proteins together with other proteins identified in previous studies were further evaluated by developing multiplexed MRM assays to quantify the proteins both before and during Abatacept treatment (at 2 and 6 months).

Methods: Baseline samples from 6 patients were prepared according to the FASP protocol and analysed by Q-Exactive. MS data was analysed using MaxQuant (v. 1.4.1.2.) and Perseus (v. 1.5.0.8). For the evaluation of candidate proteins Skyline (v. 3.7.0.1317) was used to develop multiplexed MRM assays for these newly identified proteins and to analyse the MRM data acquired on high sensitivity triple quadrupole mass spectrometer (Agilent 6495).

Results: 41 proteins were shown to be differentially expressed at baseline between responders (n=5) and the non-responder (n=1). Of these proteins, 15 were elevated and 26 were reduced in the non-responder. A sub-set of the candidate proteins identified here (n=41) and some proteins identified in our previous PsA related studies was used to develop an MRM assay targeting total 114 proteins. The MRM assay was developed using our stringent MRM assay standards. Six candidate proteins, ANXA1, ANXA2, S100A10, LMNA, CADH5 and MYL6 have been shown to be differentially expressed in synovial samples collected at 2 months when compared to 6 months. A further 5 proteins, ANXAS, RS18, TAGL, TRFL and HPT were differentially expressed between responders and non-responder at the 2 month time point but most importantly, these five proteins have shown a similar pattern of expression following four months of Abatacept treatment.

Conclusions: Although the small number of patient samples in this pilot study limits the biological significance of these findings, the data highlights some of the significant advantages of unbiased LC-MS/MS protein discovery and of multiplexed MRM assays. These advantages include reproducible and robust coverage of a large number of proteins in small synovial tissue samples and a workflow that supports rapid development of optimised multiplexed assays targeted to proteins of interest.

REFERENCES:

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