2 IDENTIFICATION OF SHARED CITRULLINATED IMMUNOLOGICAL TARGETS IN THE LUNGS AND JOINTS OF PATIENTS WITH RHEUMATOID ARTHRITIS

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Background The authors have previously demonstrated that smoking induces citrullination in the lungs of healthy smokers and they know that anticitrullinated protein antibodies (ACPA) develop in rheumatoid arthritis (RA) patients many years before disease onset. It was hypothesised that shared citrullinated targets are present in the lungs and joints of RA affected individuals and sought to investigate this by full-proteome analysis of synovial and lung biopsies of RA patients.

Material and methods Proteins were extracted from synovial (n=7, five females and two males, median age 58, 66.7% ACPA positive) and lung (n=6, four females and two males, median age 63, 66.7% ACPA positive) biopsies of RA patients. Synovial biopsies were obtained at the time of open surgery from patients with long-standing RA (mean disease duration 24 years). Large bronchi biopsies were obtained by bronchoscopy from patients with newly diagnosed RA (three smokers and three non-smokers) with symptom duration less than 1 year. The proteins were reduced, alkylated and digested with Lys-C, separated by reverse-phase nanoflow-chromatography and analysed by LTQ-Velos-Orbitrap using multiple fragmentation methods. The data were searched against the human International Protein Index database using the Mascot search engine and all citrullinated peptides were manually verified. The degree of modification was quantified manually. The final results were expressed as ratios of citrullinated versus non-modified peptides.

Results Over 3300 peptides and 500 proteins were identified in the different samples. The overall protein profiles varied between patients. Five of the identified proteins in the synovium (in total eight sites) and four in the lungs (in total four sites) contained citrullinated residues. Two vimentin derived citrullinated peptides were present in a majority of synovial and lung biopsies with slightly higher citrullinated/unmodified peptides ratios in smokers compared to non-smokers (median ratio of 0.03 in smokers and 0.02 in non-smokers for one of the peptides and a median ratio of 4.5 in the smokers and 0.04 in the non-smokers for the second vimentin peptide). While non-modified and citrullinated fibrinogen α-chain derived peptides were present in various amounts in the synovium, only the unmodified sites could be detected in the lungs of a subset of the patients (three out of six).

Conclusions The authors demonstrate the presence of shared in vivo citrullinated proteins in the joints and lungs of RA individuals, providing further support for the important pathogenic link between joints and lungs in development of RA.