transcriptional process involved in the RNA maturation. Recent studies have revealed that a pathological deregulation of the spliceosome is associated to several human diseases. Yet, the spliceosome alterations and their modulation in therapeutic response have not been described in AS

Objectives: 1) To evaluate the potential deregulation of the spliceosome in AS leukocytes and their involvement in the disease pathophysiology. 2) To analyse the *in vivo* effects of anti-TNF drugs on the spliceosome components of AS leukocytes

Methods: Thirty two AS patients and 29 healthy donors (HDs) were included in a cross-sectional study. Eight AS patients were selected for a three-month longitudinal study of response to anti-TNF α therapy. Disease activity was determined by BASDAI index and, CRP and ESR levels. Physical function was measured by the BASFI index, spinal mobility by the BASMI index, and structural damage by the mSASSS. The expression of selected components of the major-(n=12) and minor-spliceosome (n=4), and splicing factors (n=28) was evaluated in purified leukocyte by Fluidigm methodology; in parallel, inflammatory marker expression was determined by RT-PCR

Results: Compared to HDs, a significant deregulation in the expression of splicing factors and spliceosome components was found in lymphocytes, monocytes and neutrophils from AS patients, being neutrophils which displayed the highest number of altered molecules. Interestingly, a specific altered profile of spliceosome members was observed when compared lymphocytes (U1, U4, U5, SRSF6), monocytes (CELF4, ESRP2, RBM3, SRSF3, TIA1) and neutrophils (FBP11, SF3BTV1, U6, U12, PTB, RBM17, MAGOH, SRSF5, SRSF10). Correlation studies revealed that inflammatory profile, disease activity (CRP, ESR, BASDAI) and structural damage (BASMI, mSASSS) were associated to the alteration of a vast number of spliceosome components in all the leukocyte subsets evaluated. In addition, the BASFI index correlated with the expression of SKIP and U6atac in neutrophils.

Anti-TNF α treatment of selected AS patients reversed the altered expression of several spliceosome components and splicing factors in PBMCs (UA2F2, nSR100) and neutrophils (ESRP1, NOVA1, SND1, SRM160, SRSF1, CUGBP). Association studies demonstrated that disease remission was associated with reversing the altered expression of a high number of the spliceosome molecules

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- [2] Anti-TNF α therapy may reverse, at least partially, the altered expression of several spliceosome components and splicing factors. Alteration of the spliceosome may provide new biomarkers for disease and therapeutic response in AS. Funded:JA PI-0139-2017, ISCIII (RIER RD16/0012/0015)

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FRI0158 PROSTAGLANDIN E2 AND ITS RECEPTOR SUBTYPE EP4 ARE INVOLVED IN ANKYLOSING SPONDYLITIS DISEASE PROGRESSION

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Background: Single Nucleotide Polymorphisms (SNPs) in PTGER4 were found to be associated with Ankylosing spondylitis (AS) in GWAS. PTGER4 codes for the prostaglandin-E2 receptor EP4. PGE2/EP4 interaction can affect bone formation and inflammation.

Objectives: We studied serum PGE2 levels and SNPs in PTGER4 in relation to spinal fusion in AS patients. We also evaluated the interaction of smoking, PGE2 and EP4 in driving IL23 production and ILC3 functions.

Methods: Patients diagnosed with AS using the modified New York criteria and followed prospectively using a standardised protocol, were included in this study. Biological samples including serum, gut, synovial and bone marrow (BM) samples, DNA and RNA were stored and radiographs of the spine obtained every two years to assess progression. ELISA for Serum PGE2 and immunohistochemistry tissue expression of PTGS1, EP4 and pCREB were performed. Radiographs were scored by mSASSS. Patients with an increase of ≥ 1 mSASSS unit/year on follow up were deemed progressors. Five PTGER4 SNPs, associated with AS or related diseases, call rate above 90%, MAF >0.1 and not in LD above 0.8, were studied. Immune cell subsets from PBMCs were analysed for surface expression of the EP4 receptor. Additionally, PBMCs were incubated with nicotine, PGE2, or EP4 agonist to evaluate changes in ILC3 percentages and to determine cytokine expression by flow cytometry and RT-PCR.

Results: Serum PGE2 levels were significantly higher in AS progressors (n=88) than in non-progressors (n=101) (p<0.001). In multivariable regression analysis, there was significantly more progression in patients with higher baseline mSASSS

(B=0.02; p=0.01) and serum PGE2 (B=0.001; p=0.002), but lower progression with longer TNF inhibitor use (B=-0.01; p=0.03). There was a trend towards higher progression with higher baseline ESR (B=0.012; p=0.08). 3). A total of 172 AS patients had DNA and X-ray data for analysis. Patients with CC genotype of PTGER4 SNP rs6896969 were significantly more likely to progress compared to AA/AC (OR: 2.45, 95% CI: 1.3 to 4.6; p=0.006). Progressors tended to more likely be homozygous for the major allele G of the rs4957341 SNP (OR 2.1; 25% CI: 0.98-4.35; p=0.058). Increased expression of EP4, PTGS1 and pCREB were observed in the gut, BM and synovial samples of AS patients. EP4 expression was upregulated in circulating AS monocytes and ILC3, especially smokers, and the percentage of EP4⁺ monocytes and ILC3 correlated with the BASDAI. Sorted EP4⁺CD14⁺ cells showed a higher expression of CREB and IL-23 and *in vitro* stimulation of monocytes with PGE2 increased IL-23 expression, demonstrating the functional relevance of EP4 expression on monocytes. The expression of EP4 is dependent on the transcription factor AP-2a (TFAP-2a). *In vitro* stimulation of monocytes with nicotine induced a significant monocyte over-expression of EP4 and TFAP-2a. Finally, PGE2 stimulation of isolated PBMC from AS patients significantly expanded IL-23-producing ILC3.

Conclusions: PGE2 and its receptor EP4 are significant players in AS driving both inflammation and spinal fusion. The complex interaction of smoking, prostaglandin pathway upregulation and IL-23 dependent innate immune activation can contribute to the pathogenesis of AS

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FRI0159 ANTIBODIES TO POST-TRANSLATIONALLY MODIFIED COLLAGEN II IN SPONDYLOARTHRITIS

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Background: Spondyloarthritis (SpA) are a group of rheumatic diseases with either predominantly axial inflammatory symptoms of the spine and sacroiliac joints, or predominantly peripheral arthritis. The most common axial SpA (axSpA) are non-radiographic axSpA and in particular ankylosing spondylitis. The current gold standard diagnostic criteria for axSpA are clinical symptoms, radiology, MRI or ultrasound according to Assessment of SpondyloArthritis international Society (ASAS) criteria.¹ We have previously showed that antibodies to oxidative post-translationally modified collagen type II (oxPTM-CII) are present and specific in RA patients whether ACPA positive or negative.²

Objectives: The aim of the current study was to test the presence of antibody to oxidised collagen type II (CII) in axSpA, based on the hypothesis that spinal inflammation in axial SpA results in oxidative posttranslational modification (oxPTM) of axial joints cartilage matrix proteins such as CII with the consequently formation of neoepitopes and a secondary humoral autoimmune response.

Methods: CII was oxidised by exposing CII to ribose and hypochlorous acid. Levels of antibodies specific to native CII and CII post-translationally modified by oxidants (oxPTM-CII) was assessed by enzyme-linked immunosorbent assays (ELISA) in serum samples obtained from patients with axSpA (n=67) in remission and axSpA patients (n=14) non in remission. Reactivity in axSpA was compared to reactivity in samples from patients with predominantly peripheral arthritis such as psoriatic arthritis (PsA, n=54), undifferentiated arthritis (UA, n=49) and early rheumatoid arthritis (ERA, n=60). As a control we used fibromyalgia (FM, n=19) and healthy subjects (HC, n=70). The specificity of the binding was further assessed by competitive ELISA and western blot.

Results: Stronger binding to oxPTM-CII was observed in serum samples from axSpA patients, the positivity was 72% for patients in remission and 86% for patients not in remission (86%) compare to positivity in PsA group (33%), UA group (35%) and FM group (16%), (p<0.0001). Interestingly, binding of axSpA samples was similar to binding of serum samples from ERA (95%). Binding to ROS-CII was directed to a range of ROS-CII fragments between 25 and 150 kDa.

Conclusions: Formation of oxPTM-CII neoantigens in the inflamed axial joints results in an immune response that elicits antibodies specific to oxPTM-CII. Once established in future studies, antibodies to oxPTM-CII may be developed as potential biomarker for axSpA.

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