differences disappeared. Adverse events were mostly mild and comparable between groups.

Conclusion: Six-week treatment with low-dose oral prednisolone led to a substantial improvement of symptoms in patients with painful hand OA and signs of inflammation. This trial provides evidence that local inflammation is a suitable target for drug-treatment in hand OA.

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Systemic sclerosis, myositis and related syndromes – etiology, pathogenesis and animal models

OP0181

MOLECULAR CHARACTERIZATION AND STRATIFICATION OF IDIOPATHIC INFLAMMATORY MYOPATHIES: ON THE BASIS OF SKELETAL MUSCLE TRANSCRIPTOME STUDY

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Background: Idiopathic inflammatory myopathies (IIM) are a group of complicated heterogenous autoimmune diseases, to date, little is known about its skeletal muscle transcriptomic features.

Objectives: Here, we performed skeletal muscle RNA-sequencing (RNA-seq) to discover the global muscle transcriptional signature of IIM based on myositis-specific antibodies (MSA) profiles and investigate the potential molecular pathway of IIM.

Methods: Muscle specimen were taken from 60 patients with IIM, 6 patients with non-IIM myopathies and 9 healthy controls. The serum and PBMC samples were also obtained from the IIM patients at the time of muscle biopsy. For RNA-seq, IIM was dissected into eight groups based on their MSA profiles: MSA and ANA negative (n = 4), anti-synthetase antibodies positive (n = 13), -MDA5 positive (n = 6), -NXP-2 positive (n = 7), -TIF-1γ positive (n = 10), -SRP or anti-HMGCR positive (n = 6), -Mi-2 positive (n = 7), MSA negative but anti-Ro-52 positive (n = 7). RNA from muscle specimen were extracted according to manufactory guide and sequenced using Illumina HiSeq2500. Quantitative real-time reverse transcription-polymerase chain reaction (qRT-PCR) was performed on sequencing cohorts and expanding cohorts to validate the results of RNA-seq. Immunohistochemistry was also performed on muscle biopsy to determine the MxA expression in different MSA subgroups.

Results: To define the global muscle signature of IIM, all IIM samples were compared to NC and total of 1637 transcripts were differentially expressed (log2 Fold Change > 1, Padj < 0.05). Unsupervised hierarchical clustering of these differentially expressed transcripts (DETs) revealed a prevalent interferon (IFN) signature and showed that 68 interferon-stimulated genes (ISGs) were significantly up-regulated in IIM. Then these 68 ISGs were used to cluster different MSA subgroups and distinct ISG expression was found. The mRNA expression levels of several ISGs (MX1, IFIH1, LAMP3, CMPK2, HERC6) in sequencing cohorts and expanding cohorts also confirmed the diverse ISG expression between different MSA subgroups. An IFN signature scoring system was established to quantify the IFN activity and subsequently IIM could be classified into IFN-Dominant, IFN-Moderate and IFN-Weak respectively based on the IFN intensity and different MSA subgroup. Moreover, the IFN-Dominant group showed much higher MxA expression on muscle biopsy than the IFN-Moderate and IFN-Weak group by immunohistochemistry.

Conclusion: We revealed a prominent IFN signature and MSA-based ISG expression heterogeneity in IIM through muscle transcriptomics. Preliminary

results showed that the IFN muscle signature may play a predominant role in some subgroups but not all IIM groups in the pathogenesis of IIM.

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OP0182

SYNTHETIC PEPTIDES TARGETING CD206 INHIBIT PATHOGENIC MACROPHAGES IN SYSTEMIC SCLEROSIS

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Background: In systemic sclerosis, activated macrophages having M2-like properties are believed to contribute to the fibrotic pathology by secreting profibrotic factors such as TGFβ. Certain synthetic peptides (10-12mers) studied here coopt the mechanism used by macrophages to detect bacteria by binding to certain regions of CD206, a receptor highly expressed in the M2 macrophages, and repolarise them to an M1 phenotype.

Objectives: We aimed to determine the macrophage activation signature in SSc, assess CD206 as a biomarker of ongoing fibrotic activity, and measure the effect of the peptides on macrophage activation and macrophage-fibroblast cross-talk. Methods: sCD206 was assayed in plasma (n=50 healthy, 50 limited SSc, 50 diffuse SSc), and suction blister fluid (BF) obtained over active lesions by ELISA. sSIGLEC (monocyte interferon signature) and IL-31 (Th2 signature) were assayed for comparison. Cell surface CD206 and DAMP receptor P2X7, were assayed by flow cytometry. The macrophage activation signature was investigated further by qPCR for inflammatory M1, as well as M2-like gene expression (*IFNγ*, *Arg1*, *CD2106*). Macrophage-fibroblast cross talk was assessed using media transfer following heat activation to SSc dermal fibroblasts assayed by qPCR for collagen I. The macrophage secretome was determined by Luminex and ELISA.

Results: CD206 was significantly elevated in SSc BF (SSc median sCD206 42, HC 31 pg/ml, p<0.041). Plasma sCD206 was raised in diffuse versus limited SSc (P<0.0103) and was correlated with ESR (R=0.364, p<0.009) and sSIGLEC (R=0.244, p<0.05), but not disease duration or IL-31. By flow cytometry both CD206 and P2X7 were highly expressed by SSc macrophages (mean fluorescence SSc, 776.1 SD=409.1, 724.4 SD=455.3 vs HC 632.2 SD=73.7, 472.9 SD=25.4), correlating with modified Rodnan Skin Score (mRSS) (p<0.05, r=0.51). Double positive P2X7 and CD206 cells were seen in a subgroup with higher mRSS. Four RP peptides (RP182, 185, 832 & 837) were assessed for effect on growth of SSc and control macrophages. In general, the RP peptides selectively inhibited SSc macrophage growth, with RP185 and RP832 reaching significance (p<0.05) for 1 and 10μM concentrations at 96 hours. Pro-fibrotic cross-talk leading to elevated fibroblast collagen I, was characteristic of 4 out of 9 SSc macrophage cell lines examined. A mixed activation signature was identified by qPCR of the fibroblast-stimulating macrophages (elevated Arginase1, CD206 and IFNγ) but not the non-fibroblast inducing cell lines. Pre-treatment of the pro-fibrotic SSc macrophages with RP832, but not the others, eliminated the pro-fibrotic cross-talk (fibroblasts treated with SSc macrophage media mean collagen I, 1995 (SEM 149), RP832 treated macrophages 1551 (SEM 133) p<0.038 relative expression units, paired t test), and suppressed the macrophage activation signature (reduced mean Arg1 p<0.030, CD206 p<0.058, IFNγ p=0.058, paired t test). Secretome analysis confirmed the mixed activation signature of SSc macrophages including elevated total TGFβ, PDGF-BB, sCD40L as well as inflammatory factors IL-6, IL-1β, TNFα and type I cytokine IFNγ. Treatment with RP 832c reduced TGFβ in 6 out of 9 SSc macrophage cell lines but this did not reach statistical significance.

Conclusion: A macrophage activation signature is identified in SSc patients, in proportion to the severity of disease. A mixed activation signature with inflammatory as well as pro-fibrotic M2-like properties is seen. RP peptides, which target the cells via CD206, reduce the activation signature and inhibit pro-fibrotic cross talk in these cells.

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Shareholder of: Riptide Bioscience, Jesse Jaynes Shareholder of: Riptide Bioscience, James Stanway: None declared, Bahja Ahmed Abdi: None declared, Nikita Arumalla: None declared, Sarah Karrar: None declared, Sian Morris: None declared, Christopher Denton Grant/research support from: GlaxoSmithKline, Inventiva, CSF Behring, Consultant for: Roche-Genentech, Actelion, GlaxoSmithKline, Sanofi Aventis, Inventiva, CSL Behring, Boehringer Ingelheim, Bayer, David Abraham: None declared, Xu Shiwen: None declared, Richard Stratton: None declared

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OP0183

EFFICACY AND SAFETY OF RIOCIQUAT IN PATIENTS WITH EARLY DIFFUSE CUTANEOUS SYSTEMIC SCLEROSIS AND INTERSTITIAL LUNG DISEASE (SSC-ILD): RESULTS FROM THE PHASE IIB RISE-SSC STUDY

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Background: Diffuse cutaneous systemic sclerosis (dcSSc) is an autoimmune connective tissue disease characterised by fibrosis and, in some patients, interstitial lung disease (ILD). Riociguat is a soluble guanylate cyclase (sGC) stimulator with vasoactive, anti-proliferative and anti-fibrotic effects. We hypothesised that riociguat may preserve lung function in patients with dcSSc.

Objectives: To evaluate the effect of riociguat on lung function in patients with early dcSSc from the multicentre, randomised, double-blind, placebo-controlled Phase IIB RISE-SSc study (NCT02283762).

Methods: Patients had dcSSc of duration ≤ 18 months, modified Rodnan skin score (mRSS) 10–22 units, forced vital capacity (FVC) $\geq 45\%$ predicted (%pred) and lung diffusion capacity for carbon monoxide (DLCO) $\geq 40\%$ pred at screening. Patients were randomised to riociguat (n=60) or placebo (n=61) in individually adjusted doses of 0.5 mg up to 2.5 mg tid. The primary endpoint was the change in mRSS from baseline to Week 52. Secondary endpoints included change in FVC%pred from baseline to Week 52. Effects on lung function (FVC%pred) were assessed in the overall population and in post-hoc analyses in patients with FVC %pred 50–75% or medical history of ILD at baseline. Between groups, differences were in least-squares [LS] means.

Results: Although the study did not meet its primary endpoint, there was a reduction in mRSS with riociguat vs placebo (–2.34; 95% CI: –4.99 to 0.30; p=0.08). There were no significant differences between treatment groups in the changes in FVC%pred (–0.20; 95% CI, –3.40 to +3.00; p=0.90) or DLCO%pred (2.01; 95% CI: –4.99 to 6.25; p=0.35) which included all patients irrespective of the presence of SSC-ILD. However, differences between riociguat and placebo were observed when patients with SSC-ILD were analysed: At baseline, 11/60 (18%) patients in the riociguat group and 12/61 (20%) in the placebo group had medical history suggesting ILD (SSc-ILD); 11/60 (18%), and 7/61 (11%), respectively, had restrictive lung disease (FVC%pred 50–75%). Results in subgroups were expressed as within-group mean change (SD). In patients with SSC-ILD, the decline in FVC%pred between baseline and Week 52 was smaller in the riociguat group (–2.7[4.0]) than the placebo group (–8.9[13.1]). The changes in DLCO%pred were –0.11 (0.22) and +0.87(0.71), respectively. In patients with restrictive lung disease, FVC %pred decreased by –8.7 (14.0) at Week 52 with placebo but was almost unchanged (+0.7[5.7]) with riociguat. The changes in DLCO%pred were +0.42 (0.85) and –0.27(0.39), respectively.

Patients with SSC-ILD receiving riociguat had lower incidences of adverse events and serious adverse events [82% (n=9) and 9% (n=1) respectively] compared with placebo [92% (n=11) and 25% (n=3) respectively] with no differences between treatment groups in the incidence of respiratory adverse events. No deaths occurred in the SSC-ILD subgroup, and no new safety signals were observed.

Conclusion: These results suggest that in an exploratory analysis, riociguat may be associated with preservation of lung function and good tolerability in patients with dcSSc and evidence of ILD on medical history.

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OP0184

PROFIBROTIC LNCRNA H19X: UNRAVELLING THE EFFECTS ON CHROMATIN REMODELING IN SYSTEMIC SCLEROSIS FIBROBLASTS

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Background: Long noncoding RNAs (lncRNAs) are noncoding transcripts involved in the regulation of gene expression in health and disease. lncRNAs function via different mechanisms either acting cis, regulating the expression of nearby genes, or in trans, modulating the expression of distant genes. We identified a novel TGF β regulated lncRNA, H19X, which was strongly upregulated in a wide variety of fibrotic disorders. Moreover, we were able to demonstrate that H19X is a key driver of myofibroblast formation and extracellular matrix (ECM) overproduction.

Objectives: To define the mode of action of H19X (cis or trans) and to assess H19X function on chromatin rearrangements that may drive myofibroblast differentiation and ECM production.

Methods: The function of H19X was investigated in SSC dermal fibroblasts (n=5) by knocking down H19X with locked nucleic acid oligonucleotides followed by TGF- β stimulation and microarray analysis with Illumina HT-12 arrays. In situ hybridization for H19X was performed using Stellaris FISH probes. Chromatin remodeling was investigated by Assay for Transposase-Accessible Chromatin using sequencing (ATAC-seq).

Results: As analyzed by microarray, none of the 16 genes belonging to the same genomic region as H19X locus was affected by its downregulation, indicating that in-cis regulation is not a major mechanism of H19X activity. Cellular localization can give a first indication about lncRNA trans function: FISH staining of SSC fibroblasts stimulated with TGF- β revealed tightly localized nuclear foci in TGF- β treated cells. H19X nuclear localization was confirmed by cell fractionation, where H19X expression was peaking in the nucleus of cells after 6h of treatment with TGF- β . We next hypothesized that H19X nuclear expression might induce chromatin rearrangements. We assessed whether chromatin changes caused by H19X knockdown might be correlated with changes in expression profile seen by microarray. Therefore, we analyzed the differences in the chromatin conformation flanking transcription start sites (TSSs) by ATAC-seq. A clear separation between the two experimental groups (scrambled vs H19X knockdown) was observed and 450 differentially accessible regions were identified (p<0.05, Log2FC>0.5).

After focusing on genes that displayed significant variations and Log2FC>0.5 for both the array and ATAC-seq analysis, eight candidate genes were found both upregulated by microarray and showed increased accessibility at their TSSs by ATAC-Seq. Similarly, three candidate genes were identified as being downregulated by microarray and showed decreased TSS accessibility by ATAC-Seq. These genes included histones HIST1H2BD and HIST1H1C, suggesting a direct regulation of chromatin organization as a mode of action for H19X. Moreover, the cell cycle progression inhibitors FABP3 and PTTG1 were pointing to a role of H19X in proliferation.