In eRA SOST rs6503475 was associated with anti-CarP (AOR 9.4 [95% CI 1.1-10.8] p=0.037), LRP-5 with former smoking (AOR 8.6 [95% CI 2.0-36.4] p=0.004), additionally, in patients with a combination of at least three SNPs with a lower frequency of anti-Carp peptide (AOR 0.99 [95% CI 0.02-6.08], p=0.014), meanwhile a combination of at least five SNPs with a higher frequency of anti-Carp (AOR 4.7 [95% CI 1.27-17.1]) p=0.020 were observed. There were no differences in FDR group.

Conclusion: Significant associations between Wnt pathway genes variants, haplotypes, and antibody profile could reinforce evidence to relation of high titers of anti-Carp with decreased BMD in eRA patients.

Acknowledgements: Hospital Militar Central - Universidad El Bosque

Disclosure of Interests: None declared


POS0138

RHEUMATOID SYNOVIAL FIBROBLASTS DISPLAY IMPRINTED MEMORY OF THEIR SYNOVIAL ENDOTYPE WHICH CAN BE PLASTICALLY MODULATED BY B-CELLS CROSSTALK

F. Prediletto1, C. Cubbi1, E. Pontarini1, F. Rivellese1, A. Nerviani1, D. Lucchesi1, M. Calisti1, E. Corsiero1, R. Hands1, M. Lewis1, C. Pitzalis1, M. Bombardieri1.
1William Harvey Research Institute, Queen Mary University of London, Centre for Experimental Medicine & Rheumatology, London, United Kingdom

Background: Despite advances in the treatment of Rheumatoid Arthritis (RA), syntheses and biological drugs are ineffective in ~40% of patients. The origin of this refractoriness is unclear, but several clues point at the synovial microenvironment (SE) and the relative cellular heterogeneity between patients. We previously described the existence of different RA endotypes such as the lympho-myxoid LM, which is B-cell rich and the fibro-paucicellular, FPI, which is comprised of B-cells. While there is clear evidence that the coexistence between stromal and immune cells in rheumatoid joints is critical for the perpetuation of chronic inflammation and autoimmunity, it is currently unknown whether transcriptional signatures identified in synovial fibroblasts (SFs) derived from different RA endotypes are driven by “imprinted” properties of the SFs or are shaped by the interaction with infiltrating immune cells in the RA joints.

Objectives: i) to identify “imprinted” vs “inducible” RASF signatures through the comparison of freshly isolated SFs and primary established SFs cultures obtained from LM vs FPI RA synovial biopsies and ii) to investigate the identified RASF signature as predictive biomarkers of disease evolution and of response to conventional and biological DMARDs.

Methods: We performed flow cytometry and single cell RNA sequencing (sc-RNAseq) on SFs obtained from LM and FPI biopsies, in isolation or in co-culture with RA B cells. Next, supernatant has been screened trough Multiplex and ELISA. Furthermore, we compared our results to publicly available sc-RNAseq datasets on freshly isolated SFs and to our bulk-RNaseq data from clinical trials patients.

Results: Hierarchical clustering from sc-RNAseq transcriptional profiling of LM vs FPI RASF - after several cell passages - identified profoundly different gene signatures: whereby LM-RASF were characterised by genes involved in inflammation, proteoglycan formation and integrin binding. FPI-RASF were defined by genes related to collagen biosynthesis. Comparing the above signatures with those of freshly isolated RASF we identified both imprinted (i.e. maintained through several in vitro passages) and inducible (i.e. loss after long term culture) gene signatures. Notably, RA B-cells co-cultured with FPI-RASF profoundly altered the FPI-RASF transcriptional profile including the ex novo expression of gene signatures typical of LM-RASF. Consensus gene modules constructed on LM vs FPI RASF imprinted gene signatures could be tracked in longitudinal whole tissue bulk RNA-seq data obtained from both early arthritis and established RA and were associated with synovial pathotype-specific histological and clinical features. Finally, modulation of FPI-RASF related genes following B-cell depletion identified poor responders to Rituximab in the RA4R randomised clinical trial.

Conclusion: Our work demonstrates that RASFs from different endotypes display imprinted memory of their original synovial tissue when maintained in culture over several months. We also demonstrated that imprinted memory typical of RASF isolated from B-cell rich LM synovial tissues can be dynamically modulated in FPI RASF following cross-talk with RA B cells. Finally, consensus gene modules based on FPI vs LM RASF gene signatures were able inform on response/resistance to targeted biologic therapies.

REFERENCES:

Disclosure of Interests: None declared


POS0139

RELATIONSHIP BETWEEN SYNOVIAL FLUID IMMUNE CELL PHENOTYPES AND CLINICAL OUTCOMES IN PATIENTS WITH KNEE OSTEOARTHRITIS

M. Trajceva1, E. Krieger1, Z. Mikułków1, J. Savara1, M. Kudlik2, J. Gallo1 on behalf of OLGLEN, 1Palacký University Olomouc, Department of Immunology, Olomouc, Czech Republic; 2University Hospital Olomouc, Department of Immunology, Olomouc, Czech Republic; VSB - Technical University of Ostrava, Department of Computer Science, Ostrava, Czech Republic; 3University Hospital Olomouc, Department of Orthopaedics, Olomouc, Czech Republic

Background: Knee osteoarthritis (KOA) is a highly heterogeneous and multifaceted disease with many clinical phenotypes that often overlap. So far, phenotypes based on the composition of immune cells in synovial fluid (SF) have not yet been defined, although these cells, their activation and the mediators they produce play a central role in the pathophysiology of OA.

Objectives: This study aimed to investigate the relationship between SF-derived immune cells and SF protein patterns in patients with KOA and its relationship to disease trajectory. Special emphasis was given to chemokine receptor expression on macrophages.

Methods: Immune cell phenotype and protein pattern from 119 KOA patients were analysed using flow cytometry. KOA phenotypes were determined by multivariate network analysis and related to clinical outcome 3-6 months post-sampling. The chemokine receptor pattern on macrophages was analysed using the FlowSOM algorithm and verified by manual gating.

Results: Four KOA-phenotypes were detected based on the distribution of T-lymphocytes, monocyte-macrophage lineage cells and activated CD8+ T-lymphocytes. The “healing” phenotype (n=17) had a high proportion of T lymphocytes, but low NK cells, monocyte-macrophage lineage and neutrophils, showing low lymphocyte percentage and T -lymphocyte activation. From the “inflammatory progressive” phenotype (n=36) with a high proportion of activated lymphocytes, high NK cells and monocyte-macrophage lineage representation yet low level of T-lymphocytes only 39% of patients improved during follow-up. The phenotypes showed differences in CXCL10 expression, with high levels in the “healing” KOA1 compared to the “inflammatory progressive” KOA4 phenotype (1106 vs 126 pg/ml, p=0.001). In general, high CXCL10 levels were associated with improved disease trajectory compared to patients with low CXCL10 levels.

Disclosure of Interests: None declared

worsening symptoms (339 vs 222 pg/ml, p=0.002). CXCL10 levels in patients with improved symptoms showed a decreasing trend between phenotypes from KOA > KOA2 > KOA3 > KOA4. Regarding macrophages, low expression of chemokine receptors CXCR4 and CCR7 on macrophages was associated with improved symptoms regardless of KOA phenotype.

Conclusion: We identified four KOA phenotypes differing in immune cell percentage and activation associated with different clinical trajectories. Low expression of chemokine receptors CXCR4 and CCR7 on macrophages and high CXCL10 in SF was linked to KOA symptom improvement. How these phenotypes can influence treatment choices and disease progression deserves further investigation.

Acknowledgements: None declared

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2022-eular.7485

Predicting outcomes in systemic sclerosis: stratification by auto-antibodies or combining cutaneous subsetting in the EUSTAR cohort


Objectives: The aim of this study was to investigate the predictive value of autoantibodies in SSc patients from the EUSTAR cohort. The EUSTAR cohort is a wide collection of SSc patients recruited in 25 European rheumatology centers. EUSTAR patients were recruited for blood sampling (n = 30). Disease activity was measured using the SSc-30 index. Further information includes patient demographic data, self-reporting of cutaneous subset in the time period of the disease evolution, laboratory data about auto-antibodies (antinuclear, anti-cytoplasmic, anti-Scl70, anti-RNA polymerase III, anticytomegaly antibodies), and clinical data of a 10-year period. The endpoint of interest was KOA symptom improvement (NRI). Missing data were imputed through multiple imputation.

Methods: Patients from the EUSTAR database were classified either as (i) limited cutaneous, diffuse cutaneous or sine scleroderma (based on the recording made by the treating physician) or (ii) according to autoantibodies with the following subclassifications: (1) no specific autoantibodies, (2) isolated ANA, (3) anti-centromere antibodies, (4) anti-Scl70 antibodies and (5) anti-RNA polymerase III antibodies or (iii) according to combination of cutaneous subset and specific antibodies are used: anti-centromere, anti-Scl70 and RNA polymerase III antibodies.

Results: In all, 10,711 patients were included: 84.6% females, mean age: 54.4±13.8 years, mean disease duration: 79.8±8.2 years. In the prospective analysis (n=6,467 to 7,829 according to the cohort), after a mean follow-up of 56 months and a mean of three visits per patient, we did not identify any difference in AUC between the cutaneous-based model and the antibody-based model for prediction of OS and disease progression. However, the NRI showed a significant improvement in prediction of OS (0.57 [0.46-0.71] vs. 0.29 [0.19-0.39]) and disease progression (0.36 [0.29-0.46] vs. 0.21 [0.14-0.28]) at 4 years using the antibody-based model. Regarding prediction of each organ involvement in longitudinal analyses, the antibody-based model showed better performance than the cutaneous-one for renal crisis (AUC: 0.719 [0.696-0.742] vs. 0.664 [0.643-0.685]), with highest association observed with anti-RNA polymerase III (OR: 7.47 [1.63-34.24], p=0.010). Similarly, the antibody-based model was better than the cutaneous model in predicting lung fibrosis (AUC 0.719 [0.715-0.742] vs. 0.653 [0.647-0.659]) and restrictive lung fibrosis (AUC 0.759 [0.749-0.766] vs. 0.711 [0.707-0.721]) which were both associated with anti-Scl70 antibodies (OR: 9.29 [8.17-10.55] and 7.92 [5.37-11.69], respectively, p<0.0001 for both). Although there was no difference in the AUC to predict digital ulcers, NRI showed an improvement using the antibody-based model (0.31 [0.29-0.33] vs. 0.24 [0.22-0.26]) with the highest association with anti-Scl70 antibodies (OR: 3.57 [2.68-4.75], p<0.0001). The two models had similar performances in assessing occurrence of intestinal involvement, heart dysfunction or elevated sPAP.

Conclusion: Auto-antibody status outperforms the common cutaneous subsetting to risk-stratify SSc patients in the EUSTAR cohort. This easily performed subclassification using autoantibodies specific status can be used by clinicians to risk-stratify their patients and to adapt disease monitoring in routine practice.

Disclosure of Interests: Muriel Elhai Speakers bureau: BMS outside of the submitted work, Marouane Boubaya: None declared, Nanthara Srithanarn: None declared, Alexandre Balbir-Gurman: None declared, Elise Siegert: None declared, Eric Hachulla: None declared, Jeska de Vries-Bouwstra: None declared, Gabriela Riemekasten: None declared, Jörg H.W. Distler: None declared, Douglas Weale: None declared, Eduardo Rosato: None declared, Francesco Del Galdo: None declared, Fabian A Mendoza: None declared, Daniel Furst Consultant of: Abbvie, Novartis, Pfizer, R-Pharm, Grant/research support from: Emerald, Kadmon, PICORI, Pfizer.Prometheus, Talaris, Mitsubishi, Carlos De la Puente Bujidos: None declared, Anna-Maria Hoffmann-Vold: Speakers bureau: Actelion, Boehringer Ingelheim, Jansen, Lilly, MediScand, Merck Sharp & Dohme, Roche, Consultant of: Actelion, ARZX, Bayer, Boehringer Ingelheim, Jansen, Lilly, Mediscand, Merck Sharp & Dohme, Roche, Grant/research support from: Boehringer Ingelheim, Armando Gabrielli: None declared, Olivier Distler: None declared, Issam Fare` Consultant of: Abbvie, Novartis, Pfizer, Grant/research support from: Actelion, Boehringer Ingelheim, Corus, CSL Behring, 4P Science, Galapagos, Glenmark, Horizon, Inventiva, Kymera, Lupin, Millenyi Biotec, Mitsubishi Tanabe, MSD, Prometheus, Grant. Sanofi-Aventis: Grant/research support from: Kymera, Mitsubishi Tanabe, Boehringer Ingelheim, Coralie Bloch-Queyrat: None declared, Yannick Allanore Consultant of: Actelion, Bayer, BMG, Boehringer-Ingelheim, Inventiva, Roche, Sanofi-Aventis, Grant/ research support from: Actelion, Bayer, BMS, Boehringer-Ingelheim, Inventiva, Roche, Sanofi-Aventis.


To produce mitochondrial ROS and participate in SLE pathogenesis

M. Scherlinger1,2, V. Guillotin1,4, P. Vacher1, J. Douchet2, E. Lazaro1,6, C. Riche3,4, P. Bianco1,4, *Strasbourg University Hospital, Rheumatology, Strasbourg, France; 2Beth Israel Deaconess Medical Center (BIDMC), Rheumatology, Boston, United States of America; 3CHU Bordeaux - Site Pellegrin, Intensive Care, Bordeaux, France; 4ImmunoConcept Lab CNRS UMR 5164, UMR S164, Bordeaux, France; 5INSERM, U1218, Bordeaux, France; 6CHU Bordeaux - Site Pellegrin, Rheumatology, Bordeaux, France; 7CHU Bordeaux - Site Pellegrin, Immunology, Bordeaux, France

Background: In patients with active systemic lupus erythematosus (SLE), circulating platelets have an activated phenotype characterized by the expression of P-selectin (CD62P). We have shown that in human SLE, platelets interact with T regulatory cells and repress their immunosuppressive functions through a P-selectin/CD15s-dependent interaction (1). Preliminary results showed that neutrophils express high level of CD15s, predicting a possible platelet/neutrophil interaction in SLE patients.

Objectives: Investigate platelet/neutrophil interaction in human SLE and evaluate its impact on neutrophil functions, and lupus pathogenesis.

Methods: Patients with SLE responding to the 2019 ACR/EULAR criteria were recruited for blood sampling (n = 30). Disease activity was measured using...