Abstract OP0153 – Table 1

	Overall	Patients with infection	Respiratory	Gastrointestinal	Genitourinary	Musculoskeletal	Sepsis	Skin/Soft Tissue	Other
Age, years (SD)	57.3 (12.5)	61.5 (11.7)	60.0 (11.5)	61.7 (11.1)	59.8 (11.9)	58.7 (10.5)	63.5 (11.2)	57.9 (11.9)	55.3 (11.4)
Female (%)	75.7	72.6	74.8	77.4	89.2	70.2	76.6	79.5	83.3
Baseline DAS28 (SD)	6.2 (1.2)	6.4 (1.2)	6.3 (1.2)	6.3 (1.1)	6.3 (1.2)	6.5 (1.2)	6.4 (1.1)	6.4 (1.1)	6.3 (1.1)
Baseline HAQ (SD)	1.9 (0.7)	2.1 (0.6)	2.0 (0.6)	2.1 (0.6)	2.1 (0.6)	2.1 (0.6)	2.2 (0.5)	2.0 (0.6)	1.9 (0.6)
Steroid use,n (%)	8346 (38.2)	2632 (49.4)	2832 (43.8)	493 (51.5)	1226 (44.5)	390 (51.6)	316 (57.3)	1583 (45.2)	1267 (39.6)
Current smoker, n (%)	4682 (21.7)	1159 (21.9)	1422 (22.1)	165 (17.3)	452 (16.4)	186 (24.8)	122 (22.4)	692 (19.9)	573 (18.0)
RhFactor positive, n (%)	13,340 (63.2)	3533 (67.5)	4176 (66.1)	626 (66.2)	1737 (64.6)	527 (71.4)	361 (66.1)	2241 (65.6)	2003 (64.0)
Recurrent infection rate, % per annum (95% CI)	–	12.7 (12.1–13.2)	15.0 (13.9–16.2)	10.8 (9.2–12.8)	14.5 (12.7–16.5)	10.1 (8.7–11.8)	19.7 (15.1–25.7)	11.2 (10.1–12.5)	9.1 (7.3 -11.4)
Adjusted Hazard Ratio for annual incidence of recurrent infection (95% CI)	–	–	REF	0.79 (0.65–0.95)	0.97 (0.83–1.14)	0.81 (0.67–0.96)	1.33 (1.01–1.76)	0.87 (0.77–1.0)	0.70 (0.54–0.91)

index infection, the annual rate of serious infection was 12.7% (95% CI 12.1–13.3). Respiratory infections were the most common (41.4% of all events). The system class of index infection was associated with the risk of a recurrent event; subjects who experienced sepsis had the highest risk of subsequent serious infection within 12 months:19.7%. Compared to an index respiratory tract infection, sepsis conferred a 33% increased hazard for recurrent serious infection within a year (HR 1.33, 95% CI 1.01–1.76). Increasing age was a significant predictor of infection recurrence.

Conclusions: There is a high risk of recurrent infection in RA patients with past serious infection. Work is ongoing to determine whether organ class of recurrent infection event mirrors index events and the impact of biologic treatment decisions following the index infection.

Disclosure of Interest: None declared

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Advances in RA and SpA pathophysiology

OP0154 ALTERED LYMPH NODE STROMAL CELLS DURING THE EARLIEST PHASES OF RHEUMATOID ARTHRITIS

C. Ospelt[1], E. Karouzakis[1], J. Hähnlein[2], J.F. Semmelink[2], R.E. Gay[1], P.P. Tak[2,3], D.M. Gerlag[2,4], S. Gay[1], L.G. van Baarsen[2]. *[1]Center of Experimental Rheumatology, University Hospital of Zurich, Zurich, Switzerland; [2]Academic Medical Center, Amsterdam, Netherlands; [3]Cambridge and GlaxoSmithKline, University of Cambridge, Stevenage; [4]R&D Projects Clinical Platforms & Sciences, GSK Clinical Unit Cambridge, Cambridge, United Kingdom*

Background: Lymph node stromal cells (LNSC) play a crucial role in shaping the immune response and maintaining peripheral tolerance. We developed an experimental model for studying the functional capacities of human LNSC during the earliest phases of RA and compared their cellular and molecular characteristics to LNSC from healthy volunteers.

Methods: ACPA+ RA patients (n=24), ACPA+ RA-risk individuals (n=23) and seronegative healthy controls (n=14;HC) underwent ultrasound-guided inguinal lymph node biopsy. Human LNSCs were isolated and expanded *in vitro* for cellular (flow cytometry), molecular (methylome, transcriptome and microRNA) and functional (contraction) analyses.

Results: RNA sequencing was performed on LNSC of HC (n=5), ACPA+ RA-risk individuals (n=6) and ACPA+ RA patients (n=4). Of interest, LNSC from ACPA+ RA-risk individuals and ACPA+ RA patients were more similar to each other compared with HC. Pathway analysis of commonly increased genes in RA (-risk) LNSC showed, among others, significant enrichment of pathways affecting actin cytoskeleton, focal adhesion and cell junction.

DNA methylation (Illumina HumanMethylation450 array) analyses revealed 459 differentially methylated CpG sites (DMS) in LNSC from ACPA+ RA patients (n=5) versus HC (n=4), 504 DMS between ACPA+ RA-risk individuals (n=3) versus HC and 665 DMS when comparing RA patients with RA-risk individuals (delta β-value >0.1, $p<0.05$). 34 DMS were different in both RA and RA-risk LNSC compared to healthy LNSC. 80% of these DMS were significantly hypomethylated and associated with antigen processing and presentation (HLA-DRB1), immune response and regulation of actin cytoskeleton.

Accordingly, in a gel contraction assay LNSC from ACPA+ RA-risk individuals and RA patients showed impaired collagen contraction compared to healthy LNSC. Healthy LNSC (n=5) covered 26.5% +/-2.5 of the well, while RA-risk (n=4) and RA (n=5) LNSC only covered 33.9% +/-5.9 and 30.6% +/-6.5.

Conclusions: This data point towards alterations in the cytoskeleton and antigen-processing and presentation in LNSC from ACPA+ RA-risk individuals and RA patients. Further studies are required to investigate the influence of this LNSC abnormality on immune responses.

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OP0155 MDM2-MEDIATED SUMOYLATION OF P53 CONTRIBUTES TO THE MIGRATION AND INVASION OF FIBROBLAST-LIKE SYNOVIOCYTES FROM PATIENTS WITH RHEUMATOID ARTHRITIS

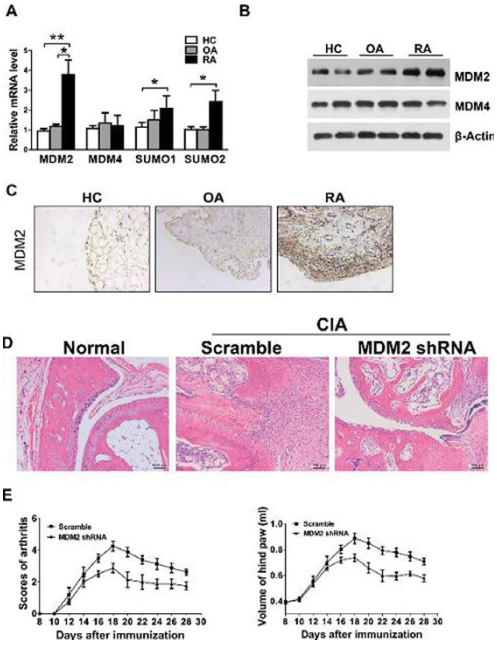
M. Shi[1,2], H. Xu[1], G. Chen[2]. *[1]Department of Rheumatology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou; [2]Department of Rheumatology, The First People's Hospital of Foshan, Foshan, China*

Background: Fibroblast-like synoviocytes (FLSs) in the synovial intimal lining are essential in the maintenance of synovial inflammation and progressive joint destruction in the development of Rheumatoid arthritis (RA). However, the precise molecular mechanisms by which this pathogenic process is regulated are not clearly defined.

Objectives: Increasing evidence indicates that p53 plays a critical role in the invasion and metastasis of cancer cells. This study aims to investigate the role of MDM2-mediated sumoylation of p53 in regulating the migration and invasion of fibroblast-like synoviocytes (FLSs) from patients with RA.

Methods: Synovial tissues were obtained from OA and RA patients, and then FLSs were separated from synovial tissues. Protein expression was measured by Western bloting or IHC staining. The sumoylation of p53 in cells was determined by immunoprecipitation. A specific inhibitor of MDM2-p53 interaction was used to inhibit the sumoylation of p53. Migration and invasion of FLSs in vitro were measured by the Boyden chamber assay.

Results: MDM2, SUMO1, and SUMO2 expression was significantly increased in the synovial tissue and FLSs of RA patients. Stimulation with TNF-α increased MDM2 expression and p53 sumoylation in RA FLSs. MDM2 shRNA inhibited p53 sumoylation, pro-inflammatory cytokines and MMPs expression, and capacity of in vitro migration and invasion in RA FLSs. Inhibition of p53 sumoylation by MDM2 shRNA promoted apotosis and reduced prolifeaation of RA FLSs. p38 MAPK signal pathway was involved in the downstream signal transduction in RA FLSs. Administration of MDM2 shRNA expressiong lentivirus attenuate the severity of rats with collagen-induced arthritis (CIA).



Conclusions: Increased MDM2-mediated p53 sumoylation contributes to aberrant aggressive behaviours of RA FLSs. Our findings suggests inhibition of MDM2 or p53 sumoylation might be a a novel therapeutic strategy to prevent synovial invasiveness and joint destruction in RA.

References:

[1] Bottini N, Firestein GS. Duality of fibroblast-like synoviocytes in RA: passive