Introduction Anti-citrullinated protein autoantibodies (ACPA) in RA patients target a wide range of modified proteins and recent findings reveal that monoclonal ACPA are cross-reactive due to recognition of shared consensus citrulline-peptide motifs. Among physiological targets of ACPA, citrullination in neutrophil extracellular trap (NET) products, have been postulated to be important.

Objectives We sought to characterize the anti-nuclear and anti-neutrophil reactivities of different patient-derived monoclonal ACPA.

Methods The study included ten recombinant single B-cell derived RA monoclonal ACPA-IgG with CCP2 reactivity from different cell subsets and compartments (1, 2). They were screened for HEP-2 ANA reactivity, and binding to apoptotic cells or stimulated neutrophils. Binding was compared to CRISPR PAD4 KO cells and neutrophils from PAD2 and PAD4 KO mice. Immunoprecipitation and mass spectrometry were used to identify modified nuclear ACPA targets, and ELISA and Western blot for mAb binding to acetylated epitopes.

Results Four out of ten ACPA clones exhibited strong binding to apoptotic cells, nuclear binding to activated neutrophils, and reactivity to NETs. Three of these were ANA positive. Another NET-reactive ACPA instead displayed a cytoplasmic binding pattern. This cytoplasmic NET-binding was PAD4-dependent, whilst nuclear-mediated NET reactivity was PAD-independent. Using apoptotic cells, acetylated histones were confirmed to be the primary targets of the nuclear reactivity, which could be explained by consensus-motif driven ACPA cross-reactivity. Specifically targeted acetylated histone peptides were identified and the anti-modified protein autoantibody (AMPA) profiles of the ACPA were found to correlate with cell binding.

Conclusions When investigating monoclonal ACPA, our novel data reveal a distinct subset of ACPA with nuclear binding patterns and AMPA activity with acetylated histones (and not citrullinated proteins) in NETs and apoptotic cells.

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P022/O02 DISTINCT MACROPHAGE PHENOTYPE AND BIOENERGETIC PROFILES IN RHEUMATOID ARTHRITIS

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Career situation of first and presenting author Student for a master or a PhD.

Introduction Synovial macrophages play a key role in RA disease progression, however, the diversity and plasticity of macrophage subsets and their metabolic profile within the joint has yet to be elucidated.

Objectives To phenotype distinct macrophage subsets within the RA joint, and determine the metabolic and inflammatory function of RA macrophages compared to healthy controls (HC).

Methods Synovial-tissue biopsies from RA, PsA and OA, obtained through arthroscopy, were digested to yield a synovial single cell-suspension. Biopsy suspensions and synovial fluid mononuclear cells were analysed using advanced flow-cytometry with the following antibody panel (CD40,CD45,CD64,CD68,CD163,CD206,CD253). CD14+ monocytes were sorted from RA and HC bloods and differentiated/polarized into M1/M2 macrophages. Inflammatory (IL-8,-MCP-1,-IL1b,-CCR5,-IRAK1,-OSM) and metabolic (HIF1a,-PFKFB3,-PKM2,-LDHA,-HK2) markers were measured by RT-PCR, and phagocytosis by OVA luciferase-yellow assays. Glycolysis (ECAR) and oxidative phosphorylation (OCR) were quantified by Seahorse -XFE- technology.

Results RA synovial-tissue and fluid CD68+ macrophages displayed markers typical of both M1(CD40+CD253+) and M2 (CD206+CD163+). A significant increase in frequency of CD68+ and CD64+ macrophages in synovial-tissue compared to fluid was observed (p<0.05), with significant increases in marker expression of CD40,CD163,CD206 (p<0.07). A spectrum of macrophage-subtypes within the inflamed joint was observed, with significant enrichment of a dominant double positive CD206+CD163+ macrophage subtype in the synovial-tissue versus synovial fluid demonstrated (p<0.05). Increased frequency of CD206+CD163+ macrophages and higher expression of activation marker CD40 were demonstrated in RA synovial-tissue compared to PsA and OA. M1 macrophages demonstrate a pro-glycolytic phenotype with significant increases in HIF1a,-HK2,-PKM2,-and PFKB3, compared to M2, effects exacerbated in RA macrophages compared to HC. In parallel, using seahorse-technology RA M1 and M2 macrophages displayed higher ECAR and OCR profiles, in addition to an increased ECAR:OCR ratio compared to HC (p<0.05), evidence that RA macrophages switch to a glycolytic profile. This was paralleled by increased intracellular-cytokines expression of IL-1b,-IL-6 and TNFα and genes expression of IL-8,-IL1b, OSM and MCP-1 (p<0.05). Finally, phagocytic ability of RA M1 was impaired compared to HC.

Conclusions We have identified, for the first time, a dominant macrophages subtype enriched in RA synovial-tissue. Furthermore, RA M1/M2 have distinct metabolic profiles associated with differences in key inflammatory mediator and phagocytosis function.

Disclosure of Interest None declared.

P023 TENOSYNOVITIS AND HLA-SE PREDICT ARTHRITIS ONSET IN ACPA-POSITIVE INDIVIDUALS AT RISK OF DEVELOPING RHEUMATOID ARTHRITIS

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Career situation of first and presenting author Post-doctoral fellow

Introduction Anti-citrullinated protein antibodies (ACPA) are predictive markers with pathological effects in rheumatoid

arthritis (RA). Previous prospective studies have used a clinical definition of arthritis. Thus, we aimed to investigate risk factors of developing arthritis in ACPA-positive subjects with musculoskeletal complaints who did not have any of clinical and ultrasound signs of arthritis.

Methods Subjects with positive ACPA-test referred from primary care to rheumatology clinic, lacking arthritis in hands and feet by clinical and ultrasound examination (according to EULAR-OMERACT synovitis definition), were recruited into the Risk-RA research program. Patient included between years 2015–2016 with clinical data up to 2017 were analysed. Blood samples from inclusion were analysed for 13 specific ACPA reactivities using a custom made ImmunoCAP ISAC microarray. Presences of HLA-SE risk gene were analysed using DR low-resolution kit.

Results 41% (27 out of 66) of the Risk RA subjects developed arthritis during a median follow up of 8 months. The rest was followed 25 months in median without any signs of arthritis. Subjects developing arthritis tended to have a higher concentration of anti-CCP, more tender joints and rheumatoid factor positivity at inclusion compared to those not developing arthritis. The number of ACPA-reactivities (mean 6 vs 3), the presence of HLA-SE (89% vs 56%) and the occurrence of ultrasound detected tenosynovitis (44% vs 5%) at inclusion were significantly increased in subjects developing arthritis compared to those not developing arthritis.

Univariate cox proportional hazards regression showed a hazard ratio (HR) for arthritis development of 1.1 for every increase in number of ACPA reactivities (95% CI 0.99 to 1.2, p 0.07); HR: 4.4 (95% CI 2.0 to 9.5, p 0.0002) for tenosynovitis and for HR: 4.9 (95% CI 1.5 to 16, p 0.01) for HLA-SE carriers. All subjects with tenosynovitis ($n=14$) prior to arthritis development were carriers of HLA-SE, except for one subject but similar to the majority this HLA-SE no-carrier also progressed to arthritis.

Conclusions Subjects with ACPA-positive musculoskeletal complaints lacking any clinical and ultrasound signs of arthritis are at high risk of developing arthritis, especially carriers of HLA-SE with tenosynovitis. The role of inflammatory spreading from tendons (synovial sheath) to synovial tissue within joints need to be further investigated.

Disclosure of Interest None declared

P024 DISTURBED SEXUAL FUNCTIONING IN FEMALE PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES

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Career situation of first and presenting author Student for a master or a PhD.

Introduction Idiopathic inflammatory myopathies (IIM) are characterized by inflammation and atrophy of skeletal muscles, pulmonary and articular involvement, which leads to functional impairment, reduced quality of life including sexual life.

Objectives The aim of this study was to assess sexual functions/quality of life and pelvic floor function in female IIM patients compared to age-/sex-matched healthy controls (HC).

Methods In total, 22 women with IIM [mean age: 55.1, disease duration: 7.9 years, dermatomyositis (DM, 8)/polymyositis

(PM, 10)/necrotizing myopathy (IMNM, 3)/inclusion body myositis (IBM, 1)], who fulfilled the Bohan/Peter 1975 criteria for DM/PM, and 22 healthy controls (mean age: 55.1 years) filled in 12 well-established and validated questionnaires assessing sexual function and pelvic floor function, fatigue, physical activity and depression. We used the following questionnaires: Female Sexual Function Index (FSFI), Brief Index of Sexual Function for Women (BISF-W), Sexual Quality of Life Questionnaire (SQoL-F), Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12), Pelvic Floor Distress Inventory Questionnaire (PFIQ7), Fatigue Impact Scale (FIS), Beck's Depression Inventory II (BDI II), Health Assessment Questionnaire (HAQ) and Human Activity Profile (HAP).

Results Compared to HC, patients with IIM had significantly higher prevalence and greater severity of sexual dysfunction (FSFI, BISF-W: in all subscales as well as total scores), dysfunction of pelvic floor (PISQ-12), and worse sexual quality of life (SQoL-F). Worse scores in IIM patients were associated with elevated muscle enzyme levels [lactate dehydrogenase: FSFI ($r=-0.524$, $p=0.0123$), BISFW ($r=-0.528$, $p=0.0115$)], greater fatigue [FIS: FSFI ($r=-0.434$, $p=0.0438$), BISF-W ($r=-0.488$, $p=0.0211$), SQoL-F ($r=-0.488$, $p=0.0070$), PISQ-12 ($r=0.643$, $p=0.0013$)], more severe depression [BDI-II: PISQ-12 ($r=0.474$, $p=0.0258$)], deteriorated quality of life [HAQ: PISQ-12 ($r=0.476$, $p=0.0252$)], and worse ability to perform physical activities [HAP: FSFI ($r=0.437$, $p=0.0417$), BISF-W ($r=0.451$, $p=0.0351$), PISQ-12 ($r=-0.494$, $p=0.0195$)].

Conclusions Women with IIM reported significantly disturbed sexual function, sexual quality of life and pelvic floor function than age-matched healthy controls. Worse scores in IIM were associated with disease activity, physical activity, fatigue, depression and quality of life.

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P025 DISTURBED SEXUAL FUNCTIONING IN FEMALE PATIENTS WITH SYSTEMIC SCLEROSIS

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Career situation of first and presenting author Student for a master or a PhD.

Introduction Systemic sclerosis (SSc) is a chronic autoimmune disease leading to various physical and psychological impairments including sexual dysfunction.

Objectives The aim of this study was to assess sexual functions/quality of life and pelvic floor function in female SSc patients compared to age-/sex-matched healthy controls (HC), and to analyze the potential impact of disease activity, fatigue, physical activity and depression.

Methods In total, 41 women with SSc (mean age: 50.9, disease duration: 5.8 years, lcSSc/dcSSc: 18/23, mRSS: 13.6, ESSG activity index: 2.5), who fulfilled the ACR/EULAR 2013 criteria, and 41 healthy controls (mean age: 50.9) without rheumatic diseases filled in 12 well-established and validated questionnaires assessing sexual function/quality of life, pelvic floor function, fatigue, physical activity and depression. We