difference in the enzyme activity between the untreated and stimulated cells in all treatment groups. However, a dose dependent decrease was observed only in case of CD14 cells. Both unsorted monocytes and monocyte sub-populations showed a significant decrease in the concentration of cortisol measured when co-incubated with carbenoxolone, indicative of the direct involvement of 11β-HSD1 enzyme in the conversion of cortisone to cortisol.

Conclusions: The results of this study showed that IL-17 induced GC insensitivity might be dependent on the reduced 11β-HSD1 enzyme activity in inflammatory conditions. We showed that the pro-inflammatory cytokine IL-17 causes a significant decrease in the 11β-HSD1 enzyme activity.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2017-eular.2681

AB0046 METABOLISM AND OSTEOARTHRITIS ARE LINKED BY ADIPOKINES

M.-L. Hülser[1], C. Schreiyäck[1], Y. Luo[2], A. Bozec[2], G. Schett[2], E. Neumann[1], U. Müller-Ladner[1]. *[1]Internal Medicine and Rheumatology, Justus-Liebig-University Giessen, Bad Nauheim; [2]Clinic of Medicine 3 - Immunology and Rheumatology, University of Erlangen-Nuremberg, Erlangen, Germany*

Background: Obesity and hyperinsulinemia are of increasing importance in the Western society. Both obesity and insulin resistance lead to changes in expression of adipokines such as adiponectin, visfatin or leptin, which appear to be immunomodulatory factors also in rheumatic diseases.

Objectives: Since osteoarthritis (OA) is often accompanied by hyperinsulinemia and obesity, we combined both mouse models (destabilization of the medial meniscus (DMM) and high-fat diet (HFD)). Here, we evaluated and correlated the systemic and local effects of both models at different states of OA development with special focus on the local/systemic expression of the adipokines adiponectin, visfatin and leptin over time.

Methods: HFD (mainly consisting of saturated fatty acids) to induce obesity and hyperinsulinemia, and ND (normal diet) as control were fed to C57Bl/6 mice for 3 months followed by surgical OA induction (time point 0). Tissues and sera were collected at different time points after DMM-mediated OA induction (4, 6, 8 weeks). Adipocytokine (leptin, visfatin, adiponectin and IL-6) serum levels were measured by ELISA. Histological stainings of the joints (H/E, safranin O, pappenheim and Masson-Goldner's trichrome) were evaluated and arthritis progress was scored. Immunohistochemical stainings of the joints were performed to evaluate the local distribution of adipokines, which were correlated to systemic adipocytokine levels and the respective arthritis score.

Results: Low systemic IL-6 levels confirmed that no acute inflammation due to surgery or infection was present in all animals. OA induction was visible at all time points, which was aggravated in HFD compared to ND mice (OA score: 4 weeks ND 0.87 vs. HFD 0.93, 6 weeks ND 1.44 vs. HFD 3.69, 8 weeks ND 1.78 vs. HFD 2.18). Systemic levels of leptin were significantly induced by HFD confirming the induction of insulin resistance, but DMM decreased leptin levels at all time points (significantly for 3 out of 6 groups, e.g. 4 weeks: HFD healthy vs. HFD DMM 18.4 ng/ml vs. 3.7 ng/ml). Interestingly, the systemic increase of adiponectin by DMM was time dependent (only 8 weeks after surgery: HFD healthy vs. HFD DMM 5176 ng/ml vs. 6149 ng/ml) but independent of diet. However, HFD in combination with DMM did not show significant effects on systemic levels of adiponectin, visfatin or IL-6.

Conclusions: HFD deteriorates OA in the DMM model. Systemic leptin levels were elevated by HFD/insulin resistance but reduced by DMM, which could not be observed for the mainly proinflammatory adipokine visfatin. Of note, systemic inflammation as shown by systemic IL-6 levels was low in all animals. The stage of OA development influences adiponectin levels, which were only increased systemically 8 weeks after surgery. In summary, systemic levels of adipokines are altered by DMM and HFD as well as the combination of both models and the analyzed adipokines show differing reactions to these factors.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2017-eular.4913

AB0047 TYPE I INTERFERON IS HIGHLY EXPRESSED IN RA SYNOVIAL FLUID AND JOINT CARTILAGE CORRELATED WITH SERUM RHEUMATOID FACTOR; A PRELIMINARY EXPERIMENTAL STUDY

M. Nakayama[1], H. Tobimatsu[1], H. Imamura[1], Y. Sakuma[1], K. Yano[1], Y. Niki[2], K. Ikari[1]. *[1]Department of Orthopedic Surgery, Institute of Rheumatology, Tokyo Women's Medical University; [2]Department of Orthopedic Surgery, Keio University, Tokyo, Japan*

Background: It was reported that type I interferon (IFN) is involved in the pathogenesis of rheumatoid arthritis (RA) [1–3], while the relevance of the IFN signature to RA disease activity and progression remains unclear. There were few reports about the expression of IFN in synovial fluid and joint cartilage.

Objectives: The aim of this study is to investigate the role of IFN in the pathogenesis of RA by means of the analysis of joint tissues of RA patients comparing with those of osteoarthritis (OA) patients.

Methods: Synovial fluid, synovia and cartilage were collected from RA and OA patients (n=10 for each) during total knee arthroplasty in our hospital and blood samples were collected just before surgery. As preoperative therapy for RA, Methotrexate (MTX) was administered to 9 patients (dose ranged (4–12mg), DMARDS without MTX to 2, biological DMARDS to 2, Prednisolone (PSL) to 6 (dose 1–5mg). Quantities of IFN alpha or beta of blood and joint fluid were measured with ELISA (PBL Assay Science, USA), and expression of IFN alpha, beta and TNF alpha of synovia and joint cartilage were measured with real time PCR. In RA patients. Serum biomarkers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), Rheumatoid Factor (RF), hemoglobin and platelet were measured and investigated correlation with the quantities of IFN of blood or joint tissues. Medication for RA were investigated as well.

Results: In blood and synovial fluid of RA patients, IFN alpha and beta were highly detected, while they were not detected in those of OA patients. The expression of IFN alpha and beta of RA cartilage were much higher than those of OA whereas they were not expressed in synovium of both RA and OA. Expression of IFN was not correlated with that of TNF alpha in RA patients. Statistical analysis revealed that RF was related with blood and joint IFN and other markers were not. Medications for RA were not correlated with IFN expression.

Conclusions: IFN was highly expressed in RA synovial fluid, joint cartilage and blood, not in OA. IFN immunotherapy has been reported to induce RA [4–5], therefore abundant IFN might induce RA and inhibit cure of RA. Our results showed that RF was related with blood and joint IFN. It can be speculated that RF might be an index of IFN regulation in RA patient, however, more samples must be investigated to prove this speculation.

References:

[1] de Padiila CML and Niewold TB. The Type I Interferons: Basic Concepts and Clinical Relevance in Immune-mediated Inflammatory Diseases. Gene. 2016; 15, 576, 14–21.

[2] Carrio JR, de Paz B, et al. IFN alpha Serum Levels Are Associated with Endothelial Progenitor Cells Imbalance and Disease Features in Rheumatoid Arthritis Patients. Plos One, 2014;9, e86069.

[3] van Holten J, Smeets TJM, et al. Expression of interferon b in synovial tissue from patients with rheumatoid arthritis: comparison with patients with osteoarthritis and reactive arthritis. Ann Rheum Dis. 2005; 64: 1780–2.

[4] Passos SE, Evangelista SPT, et al. Rheumatoid arthritis induced by alpha-interferon therapy. Clin Rheumatol. 2001;20(4):297–9.

[5] Cacopardo B, Benanti F, et al. Rheumatoid arthritis following PEG-interferon-alfa-2a plus ribavirin treatment for chronic hepatitis C: a case report and review of the literature. BMC research notes. 2013; 6:437.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2017-eular.4978

AB0048 ANTIPHOSPHOLIPID ANTIBODIES, INTERLEUKIN-6 AND TUMOR NECROSIS FACTOR-α IN ATHEROSCLEROTIC PROCESS IN PATIENTS WITH RHEUMATOID ARTHRITIS AND SYSTEMIC LUPUS ERYTHEMATOSUS

N.A. Bashlakova[1], T.D. Tyabut[2], A.E. Buglova[2]. *[1]Ultrasound Diagnostics Department; [2]Cardiology and Rheumatology Department, Belarusian Medical Academy of Postgraduate Education, Minsk, Belarus*

Background: Systemic inflammation has been postulated to be an independent cardiovascular risk factor, particularly in patients with autoimmune rheumatic disorders (ARD), such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), and is associated with accelerated atherosclerosis. There is some evidence to suggest that antiphospholipid antibodies (aPL) may also play a role in the development of atherosclerosis. However, it is few data about the relationship between these autoantibodies and inflammatory mediators in the development of atherosclerosis.

Objectives: To clarify the involvement of inflammatory mediators and aPL in the atherosclerotic process in patients with ARD.

Methods: The study included 87 female patients with ARD (RA (n=47), mean age 45,0 (33,0; 51,0) years old, disease duration 9,0 (3,0; 14,0) years, disease activity (DAS28=5,37 (4,69; 5,86) points); SLE (n=40), mean age 33,5 (27,5; 44,5) years old, disease duration 8,0 (5,0; 14,5) years, disease activity SLEDAI-2K 7,0 (4,0; 11,5) points). Sixty healthy women (mean age 40,5 (36,0; 47,0) years old) formed the control group.

The levels of high sensitive C-reactive protein (hs-CRP), interleukin-6 (IL-6), tumor necrosis factor - α (TNF-α), LA, IgG/IgM antibodies to cardiolipin (aCL), β2-glucoprotein-1(aβ2-GP1), annexin V (aAnV) and prothrombin (aPT)) were determined with ELISA. Intima-media thickness (IMT) of the carotid artery wall and the presence of atherosclerotic plaques were revealed ultrasonographically according to the described ESH/ESC Guidelines.

Results: The levels of hs-CRP, IL-6, TNF-α were significantly higher in ARD patients than in the control group, which indicates the disease activity. Furthermore, the patients with SLE had a significant correlation between IL-6 and SLEDAI-2K (r=0,471, p=0,002), TNF-α and SLEDAI-2K (r=0,499, p=0,001), whereas the patients with RA had only significant correlation between hs-CRP and DAS28 (r=0,355, p=0,031).

The concentration of IgG aCL, IgG and IgM aβ2-GP1, IgM aAnV, IgG aPT, LA were higher in patients with SLE than in the control group, and the levels of IgG and IgM aCL, IgM aβ2-GP1, IgG and IgM aAnV, LA were higher in patients with RA v.s. the control group.

We revealed a correlation between IgG aCL, IgG aβ2-GP1, IgG aAnV and TNF-α, IgG aCL and IL-6 in SLE patients, and only one between IgG aAnV and hs-CRP in RA patients. There wasn't any correlation between aPL and inflammatory mediators in the control group.
Univariate analysis has demonstrated an association of IgG aAnV with IMT (r=0,320, p=0,044) in SLE patients and positive association between TNF-α and IMT (r=0,362, p=0,028) in RA patients. Furthermore, we found an association between IL-6 and IgG aPT (r=0,426, p=0,038), TNF-α and IgG aCL (r=0,419, p=0,042) in SLE patients with carotid atherosclerosis. There wasn't any association between investigated parameters in the control group.
Conclusions: The association between inflammatory mediators and disease activity has been confirmed in ARD patients. Increased autoimmune activity has been verified both in patients with SLE and RA. It has been determined that IgG aAnV had more significance for IMT in patients with SLE, TNF-α - in RA patients. Our data can suggest that inflammatory mediators and antiphospholipid antibodies are involved in the atherosclerotic process in patients with ARD.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.5306

AB0049 NF-κB-INDUCING KINASE REGULATES LTβR-DRIVEN NF-κB SIGNALING AND INFLAMMATORY ACTIVATION OF ENDOTHELIUM

P. Kucharzewka[1], C.X. Maracle[2], J.P. van Hamburg[2], K.C. Jeucken[2], H. Olsson[1], S.W. Tas[2]. *[1]Imed Ria, AstraZeneca, Mölndal, Sweden; [2]Department of Clinical Immunology & Rheumatology and Laboratory for Experimental Immunology, AMC, University of Amsterdam, Amsterdam, Netherlands*

Background: Sites of chronic inflammation, such as rheumatoid arthritis synovial tissue, are characterized by neovascularization and often contain tertiary lymphoid structures with characteristic features of lymphoid organs such as endothelial venules (HEV), and sometimes even true germinal centers. Ligation of the lymphotoxin (LT)-β receptor (LTβR) results in activation of both canonical and NF-κB-Inducing Kinase (NIK)-dependent non-canonical NF-κB signaling in endothelial cells (ECs) and plays a crucial role in lymphoid neogenesis. Non-canonical NF-κB signaling in ECs promotes inflammation-induced angiogenesis and triggers the development of the cuboidal HEV appearance. However, the relative contribution of the individual pathways to the acquisition of leukocyte traffic-regulating properties by ECs is less well understood.
Objectives: To identify the molecular pathways by which LTβR drives inflammatory activation of ECs to promote interactions with leukocytes.
Methods: Primary human ECs were treated with LTβ or LIGHT to activate LTβR. Induction of downstream signaling pathways was assessed by western blot analysis and NF-κB transcription factor ELISA. The expression of adhesion molecules, inflammatory cytokines and chemokines, such as CXCL1, CXCL5, CXCL8 and GM-CSF in ECs was measured by RT-qPCR and cytokine antibody arrays. EC interactions with leukocytes were determined by an adhesion assay, and EC barrier integrity was assessed by a permeability assay. To repress canonical NF-κB signaling pathway, a small molecule inhibitor of IKKβ was used, and inactivation of non-canonical NF-κB signaling was achieved with siRNAs targeting NFκB2. The role of NIK in LTβR signaling was investigated using small molecule inhibitors of NIK, siRNAs targeting NIK and adenoviral vectors encoding wild type and kinase-deficient NIK.
Results: LTβR triggering in ECs resulted in activation of both canonical and non-canonical NF-κB signaling pathways and induced the expression of inflammatory cytokines and chemokines (CXCL1, CXCL5, CXCL8, MCP-1, GM-CSF, CCL5). Consistent with inflammatory activation of ECs, LTβR ligation also induced adhesion of immune cells to activated endothelium and increased permeability across EC monolayers. IKKβ inhibition completely repressed LTβR-induced inflammatory activation of ECs, indicating that this process was mediated through canonical NF-κB signaling. Interestingly, inactivation of NIK with small molecule inhibitors and siRNAs significantly decreased LTβR-induced expression of inflammatory cytokines and adhesion of immune cells to endothelium, whereas silencing of NFκB2 had no effect. This suggests that the non-canonical pathway is dispensable for NIK-dependent activation of endothelial cells through the canonical NF-kB pathway. Further analyses, including silencing of NIK and NIK overexpression, demonstrated a role for NIK in activation of the canonical NF-kB pathway by amplifying IKK complex activity.
Conclusions: These findings suggest that in addition to its pivotal role in the non-canonical pathway, NIK can serve as an amplifier of the canonical NF-κB pathway and associated inflammatory responses in ECs mediated by LTβR ligation, which may play a role in development and maintenance of chronic inflammation.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.5498

AB0050 IMPAIRED ADIPONECTIN AND LEPTIN LEVELS DURING OSTEOARTHRITIS ONSET AND DEVELOPMENT IN STR/ORT MICE

R. Giambelli, S.K. Bernini, M. Perrella, A. Grotti, R. Cavagnoli, G. Samuelli, P. Garofalo, T. Zanelli, G. Caselli, L.C. Rovati. *Rottapharm Biotech, Monza, Italy*

Background: Obesity is a risk factor for osteoarthritis (OA). In obese subjects OA develops not only in weight-bearing joints but also in non-weight-bearing joints, suggesting that dysregulated metabolism in obese patients may promote OA onset.
As obesity evolves many physiological parameters are dysregulated, including the levels of adipokine hormones such as leptin and adiponectin. For this reason, it has been suggested that adipokine levels in serum and synovial fluid are associated with a worsening of synovial inflammation and OA progression in these patients(1).
In vivo and in vitro studies show that high levels of leptin induce the synthesis of metalloproteases involved in cartilage degradation(2). Conversely, dietary-induced weight loss is associated with increased adiponectin serum levels and reduced loss of tibial and femoral cartilage volume, suggesting a protective role of adiponectin in OA.
STR/ort mice are an animal model of spontaneous OA characterized by early pathology development (at about 20 weeks) and dysregulated metabolism(3). Notably, these mice have adiponectin serum levels lower than those found in control mouse strains(4).
Objectives: To evaluate whether adiponectin and leptin serum levels are associated with OA development and/or progression in STR/ort mice.
Methods: First, we measured the time course of adipokine levels in STR/ort mice before the onset of OA (at 8, 14 and 20 weeks of age), and in age-matched CBA control mice. Then, we calculated the ratio leptin/adiponectin (L/A) in the serum of STR/ort mice during OA progression (at 20, 30 and 40 weeks). Blood samples were collected from caudal vein (time course) or from vena cava at sacrifice, when knee joints were collected, processed for histology and blindly scored according to OARSI and Mankin's methods.
Results: Adiponectin serum levels in STR/ort mice at 8, 14 and 20 weeks were significantly lower than in age-matched CBA mice. Instead, leptin serum levels in STR/ort mice were higher than in CBA strain at 14 and 20 weeks. Consequently, there was a relevant difference in the ratio L/A between the two strains, with greater L/A values in STR/ort mice at 14 and 20 weeks. (Table 1)
In STR/ort mice, the ratio L/A tended to further increase between 30 and 20 weeks (1.73±0.16 from 1.28±0.17, respectively), in parallel with the increase in OARSI scores of knee joints (11.1±1.5 vs 8.4±1.3). The histopathological score increased in STR/ort mice even between 30 and 40 weeks, but without a concomitant increase in the ratio L/A.

Adipokines levels (mean ± SEM)

Age (Weeks)	8	14	20
CBA (n=10)			
Adiponectin (µg/ml)	20.2 ± 0.7	16.0 ± 0.4	14.5 ± 0.3
Leptin (ng/ml)	1.5 ± 0.3	2.5 ± 0.3	3.1 ± 0.4
L/A	0.07 ± 0.02	0.16 ± 0.02	0.21 ± 0.03
STR/ort (n=14)			
Adiponectin (µg/ml)	9.2 ± 0.3**	7.3 ± 0.2**	6.0 ± 0.2**
Leptin (ng/ml)	3.3 ± 0.5	8.7 ± 1.3**	7.9 ± 1.1**
L/A	0.36 ± 0.05	1.15 ± 0.16**	1.28 ± 0.17**

**p<0.001 STR/ort vs CBA

Conclusions: We show for the first time that leptin serum levels and the ratio L/A in STR/ort mice are higher than in CBA mice, and that the ratio L/A in STR/ort mice increases as their histopathological scores worsen. We suggest that dysregulated levels of these adipokines may be associated or even precede OA development in this animal model.
References:
[1] King L.K. et al. Osteoarthritis and Cartilage, 2015.
[2] Bao J.P. et all. Mol Biol Rep. 2010.
[3] Uchida K. et al. Experimental Animals, 2009.
[4] Giambelli R. et al. Osteoarthtis and Cartilage Volume 24, Supplement 1, April 2016, Pages S85.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.3083

AB0051 INTERLEUKIN-6 BLOCKADE WITH TOCILIZUMAB DECREASES METALLOPROTEINASE-9 ACTIVITY IN SYNOVIAL FIBROBLASTS STIMULATED WITH SYNOVIAL FLUIDS OF PATIENTS WITH RHEUMATOID ARTHRITIS OR SPONDYLOARTHRITIS

R. Blas[1], H. Tamashiro[2], A. Munarriz[3], R. Pardo-Hidalgo[4], M.S. Di Genaro[5,6]. *[1]Centro Médico MEDICI; [2]Clínica Bolivar; [3]Centro Médico CENYR, San Luis; [4]Centro de Rehabilitación Médica CER, San Juan; [5]National University of San Luis; [6]Laboratory of Immunopathology, Multidisciplinary Institute of Biological Investigations - San Luis (IMIBIO-SL), National Council of Scientific and Technical Investigations (CONICET), San Luis, Argentina*

Background: Fibroblast-like synoviocytes (FLS) exhibit a transformed aggressive phenotype characterized by increased secretion of pro-inflammatory cytokines and matrix metalloproteinases (MMPs). Early pathological mechanisms that explain the change to an altered phenotype in FLS of chronic inflammatory arthropathies remain largely unknown. The composition of synovial fluids (SF) is very complex and strongly influences the microenvironment of joints including FLS thus representing an inseparable element of the disease. The MMP-9 is a