Objective: The purpose was to detect the susceptibility genes of RP through whole-exome sequencing (WES) in a Chinese family and deepen our understanding of the pathogenesis of RP.

Methods: A 32-year-old Chinese female proband with RP and her family in which only her mother was RP patient were recruited in the current study. The genomic DNA of 6 human subjects was extracted from the peripheral blood monocyte cells (PBMCs) and then identified gene allele mutations using WES. Candidate variants with low frequency (<0.1%) in general population and predicted deleterious on gene function were identified. Sanger sequencing was then used to validate the analysis results of WES and further validated the gene variants in 12 human subjects.

Results: 38 genes mutated were confirmed by WES among RP patients. Of them, 10 gene variants were validated by Sanger sequencing, including Collagen Type XXII Alpha 1 Chain (COL22A1) rs200464363, folliculin (FLCN) NM_1440606; c.G838A: p.E280K, glycophosphatidylinositol anchor attachment 1 (GPAA1) rs201424010, DNA ligase 3 (LIG3) rs761800558, RecQ like helicase 4 (RECQL4) rs775703895, ring finger protein 207 (RNF207) NM_207396: c.T425C:p.I142T, coiled-coil domain containing 61 (CCDC61) rs777816675, Purkinje cell protein 2 (PCP2) rs144974437, tubulin alpha 3e (TUBA3E) rs749780020 and myosin heavy chain 15 (MYH15) NM_014981.c:G4462A:p.A1448T.

Conclusions: This study confirms that coinheritance of multigene mutated may contribute to the susceptibility to RP. The candidate genes mutated we discovered are potential targets for in-depth functional studies.

REFERENCES:
[1] McAdam LP, O’Hanlan MA, Bleustone R, Pearson CM. Relapsing polyarthritis: prospective study of 23 patients and review of the literature. Medicine (Baltimore) 1976;55:193–215.
[2] Trentham DE, Le CH. Relapsing polyarthritis. Ann Intern Med 1998;129:114–122.
[3] Lang B, Rothenfusser A, Lanchbury JS, Rauh G, Breedveld FC, Urlacher VA. A novel T cell activation signature in rheumatoid arthritis: implications for disease susceptibility. Arthritis Rheum 1995;36(5):650–664.
[4] Zeuner M, Straub RH, Rauh G, Albert ED, Scholmerich J, Lang B. Relapsing polyarthritis: clinical and immunogenetic analysis of 62 patients. J Rheumatol 1997;24(1):96–101.

Adaptive immunity (T cells and B cells) in rheumatic diseases

**AB0023** SEX-BASED DIFFERENCES IN ASSOCIATION BETWEEN CIRCULATING T CELL SUBSETS AND DISEASE ACTIVITY IN UNEARTHYED RHEUMATOID ARTHRITIS PATIENTS

J. Aldridge^1, J. Pandya^1, L. Meurs^1, A. Kerstin^1, I. Nordström^1, E. Theander^1, A.-C. Lundell^2, A. Rudin^2.

1. Medicine, Rheumatology Inflammation Research, Sahlgrenska Academy, Göteborg; 2. Rheumatology, Lund University, Lund, Sweden

Background: Genetic association studies strongly support the role of CD4+ T cells in promoting RA pathology. In a cohort of untreated early RA patients, we recently demonstrated that the balance of helper T cell subsets in blood of uERA patients is skewed towards Th2 cells relative to healthy controls. RA has been shown to be a sexually dimorphic condition with current data suggesting that prevalence, disease course and treatment outcome varies between men and women.

Objectives: It is not known if sex-based disparities in immunological factors contribute to the disease process in rheumatoid arthritis (RA). Hence, we examined whether circulating T cell subset proportions and their association with disease activity differed in male and female patients with untreated early rheumatoid arthritis.

Methods: Proportions of T cell subsets were analysed in peripheral blood from 70 uERA DMARD and prednisolone naïve patients with untreated early Rheumatoid arthritis (30 females and 20 males) and in 31 healthy age-matched controls. Broad analysis of helper and regulatory CD4+ T cell subsets was done using flow cytometry. Disease activity in patients was assessed using DAS28, CDAI, swollen joint counts, tender joint counts, CRP and ESR.

Results: Multivariant factor analyses showed that male and female untreated early rheumatoid arthritis patients display distinct profiles of association between disease activity and circulating T cell subset proportions. In male, but not female, uERA patients Th2 cells showed a positive association with disease activity and correlated significantly with DAS28-ESR, CDAI and tender joint counts. Likewise, proportions of non-regulatory CTLA-4+ T cells associated positively with disease activity in male patients only, and correlated with DAS28-ESR. In contrast, there was a negative relation between Th1/Th17 subset proportions and disease activity in males only. Proportion of Th1 and Th17 cells showed a relation to disease activity in either males or females. There were no significant differences in proportions of T cell subset between the sexes in patients with untreated early rheumatoid arthritis.

Conclusions: In conclusion, our findings show sex-based differences in the association between T cell subsets and disease activity in uERA patients, and that Th2 helper T cells may have a stronger role in the regulation of disease activity in male patients.

REFERENCE:
[1] Pandya JM, et al. Circulating T helper and T regulatory subsets in untreated early rheumatoid arthritis and healthy control subjects. J Leukoc Biol 2016;100(4):823–833.

Disclosure of Interest: None declared.

DOI: 10.1136/annrheumdis-2018-eular.2596

**AB0024** IGA-EXPRESSING BM PC ARE RESPONSIBLE FOR ENHANCED PHOSPHORYLATION OF BCR-ASSOCIATED KINASES AFTER BCR STIMULATION INDEPENDENTLY OF THEIR CD19 EXPRESSION

A. Wiedemann, A.C. Lino, T. Dönner, Rheumatology and Clinical Immunology, Department of Medicine, Charité Universitätsmedizin Berlin and German Rheumatism Research Center Berlin (DRFZ), Berlin, Germany

Background: Plasma cells (PC) are considered key drivers of antibody mediated autoimmune diseases. Long-lived PC survive for years in their niches, preferentially in the bone marrow (BM) but also in inflamed tissues. 1 A subset of PC lacking expression of CD19 has been identified. 2 Better understanding of factors and pathways involved in survival and maintenance of long-lived PC is needed to find strategies to target PC in autoimmunity since targeting B cells or proliferating cells does not affect already existing PC. 3 B cell receptor (BCR) signalling is a critical mediator of B cell survival and it was shown before that IgA+ and IgM+ PC in the BM express a functional BCR suggesting a potential role for the BCR signalling pathway.

Objectives: Expression of BCR associated molecules in BM PC and the response of CD19+ and CD19- BM PC to BCR stimulation by anti-IgM/IgA/IgG was assessed to test whether these PC subsets are capable of responding to BCR mediated signals. We further investigated if the PC isotype has an impact on BCR signalling.

Methods: BM samples from patients undergoing routine total hip arthroplasty without systemic immune manifestations were stained for baseline expression of spleen tyrosine kinase (Syk) and Bruton’s tyrosine kinase (Btk) as well as for the phosphosites pSyk (Y253) and pBtk (Y223). BM mononuclear cells have been isolated, stimulated with anti-IgM/IgA/IgG and the increase of fluorescence intensity of pSyk (Y253) and pBtk (Y223) was measured by intracellular flow-cytometric analyses. In some experiments, cells have been stimulated with anti-IgA alone and stained for the isotype additionally to the pPTK staining.

Results: Whole BM stainings revealed that both CD19+ and CD19- PC express the PTKs Syk and Btk at baseline. Both PC subsets showed the ability to respond to BCR stimulation with enhanced phosphorylation of the PTKs with a clear trend to reduced responsiveness among CD19- PC. Ig staining revealed that IgA expression was identified on both membrane and intracellularly, whereas IgG was
only expressed intracellularly. Co-staining of IgA with pPTKs showed that IgA+ PC
in both subsets are responsible for enhanced phosphorylation of PTKs upon BCR stimulation
with IgA-expressing cells being exclusively responsible for this increase. Further
functional consequences of IgA expression in BM PC and autoimmunity remain to be
delineated.

REFERENCES:
[1] Manz RA, et al. Lifetime of plasma cells in the bone marrow. Nature 1997;388(6638):133–134.
[2] Tokoyoda K, et al. Organization and maintenance of immunological mem-
ory by stroma niches. Eur J Immunol 2009;39(8):2095–2099.
[3] Mei HE, et al. A unique population of IgG-expressing plasma cells lacking
CD19 is enriched in human bone marrow. Blood 2015;125(11):1739–1748.
[4] Hoyer BF, et al. Short-lived plasmablasts and long-lived plasma cells con-
tribute to chronic humoral autoimmunity in NZB/W mice. J Exp Med 2004;
199(11):1577–1584.
[5] Pinto D, et al. A functional BCR in human IgA and IgM plasma cells. Blood
2013;121(20):4110–4114.

Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2018-eular.7532

AB0025

MTOR PATHWAY ACTIVATION IN LARGE VESSEL
VASCULITIS
C. Comarmond1, A. Maciejewski-Duval1, A. Leroyer2, M. Zachariades1, A. Le Joncour1,
P. Cacoub1, D. Sadoun1.1 Internal Medicine, 2Pitié Salpêtrière, Paris, France

Background: Mammalian target of rapamycin complex 1 (mTORC 1) drives the
proinflammatory expansion of T helper (TH) type 1, TH17 cells and controls foam-
blast proliferation, typical features of large vessel vasculitis (LVV) pathogenesis.
Molecular pathways involved in arteriolar lesions of LVV are unknown.

Objectives: To analyse mTOR pathway activation in LVV (giant cell arteritis and
Takayasu arteritis).

Methods: We evaluate pathway activation in the mTORC and the nature of cell
proliferation in blood and vessels of patients with LVV compared non-inflamma-
atory aorta by using double immunostaining, western blot and flow cytometry.
Finally, using flow cytometry, we study the effect of rapamycin on T cells homeo-
statics in LVV compared to HD.

Results: Proliferation of both endothelial cells and vascular smooth-muscle cells
was shown in vascular lesions in LVV. The vascular endothelium of proliferating
aorta vessels from patients with LVV showed indications of activation of the
mTORC1 pathway in endothelial cells (SERP phosphorylation) compared to non-
inflammatory aorta (45%±48% versus 10.4% [9;7,14;9] positive SERP endothelial
cells, p<0.03). In cultured vascular endothelial cells, sera from patients with LVV stimulated mTORC1 through the phosphorylation of SERP. Activation of
mTORC was also found in TH1 and TH17 cells both systemically and in the blood
vessels. Patients with LVV exhibited a diminished SERP phosphorylation in
Tregs. Inhibition of mTORC1 pathway with rapamycin, increase Tregs and
decrease effector CD4+IFNγ, CD4+IL17 and CD4+IL21+ T cells in patients with
LVV.

Conclusions: Our results suggest that the mTORC1 pathway is involved in the
vascular lesions of LVV. Targeting mTORC pathway may represent a new therape-
utic option in patients with LVV.

Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2018-eular.7528

AB0026

TLR9 STIMULATION OF ANERGIC HCV-ASSOCIATED
ATYPICAL MEMORY B CELLS TRIGGERS RHEUMATOID
FACTOR AUTOIMMUNITY BY THE TNF-A PATHWAY
C. Comarmond, D. Saadoun. Internal Medicine, Pitié Salpêtrière, Paris, France

Background: Hepatitis C virus (HCV) infection contributes to the development of
autoimmune disorders, but the mechanisms responsible for HCV-associated autoimmunity are not well understood.

Results: Here we show that TLR9 stimulation of atypical memory (AM) B cells
from patients with HCV-associated cryoglobulinemia vasculitis induce the secre-
tion of IFNγ, TNFα but not IL17A by CD4+CD25+ effector T cells and stimulate their
proliferation. Conversely, they reduce the proliferative capacity of
CD4+CD25+CD127brightFoxP3+ regulatory T cells. TLR9-stimulated AM secrete
TNFα and IgMs with rheumatoid factor activity. We identify a transcriptional
signature specific of TLR9-stimulated AM, centred on TNFα overexpression. AM
B-cell expansions display intracranial diversity of mutated IgMs with features of anti-
gene-driven maturation. AM-derived antibodies possess rheumatoid factor activ-
ity, with each antibody clone targeting a unique epitope on the human IgG Fc
region. AM antibodies are neither polyreactive nor reactive to ubiquitous autoanti-
gens and importantly, not cross-reactive against HCV antigens including NS3 and
e2 proteins.

Conclusions: These data strongly suggest a central role for AM in defective tol-
erance of HCV-CV patients leading to TLR9 reactivation of anergic AM and produc-
tion of IgMs with rheumatoid factor activity.

Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2018-eular.7573

AB0027

SCREENING FOR ANTIBODY REACTIVITY IN EARLY
AXIAL SPONDYLOARTHRITIS IDENTIFIES NOVEL
ANTIGENIC TARGETS
D. Quaden1, P. Vandormael2, K. Corten3, J. Vanhoof2, P. Geusens4,5, V. Somers1,2
Hasselt University, Biomedical Research Institute, and
Transnationale Universiteit Limburg, Diepenbeek, 4Orthopaedic, Ziekenhuis Oost-
Limburg, 5ReumaClinic, Genic, 6Universiteit Hasselt, Biomedical Research Institute,
and Transnationale Universiteit Limburg, Diepenbeek, Belgium, 7Rheumatology,
Maastricht University Medical Center, Maastricht, Netherlands

Background: Diagnosis of axial spondyloarthritis (axSpA) is challenging since
clinical manifestations, such as inflammatory back pain, peripheral arthritis, enthe-
sitis and inflammatory bowel disease, often overlap with other disorders. Despite
the use of the genetic marker Human Leukocyte Antigen (HLA)-B27 in axSpA
patients, an appropriate serological test is still lacking. Although antibodies are
not considered to be a hallmark of axSpA, emerging evidence suggests plasma
and antibodies to be involved in the disease course.

Objectives: Our aim is to screen for antibodies reactive against antigenic targets
in plasma of early axSpA patients which may potentially result in novel antibody
markers to improve axSpA diagnosis and can enhance the assessment of dis-
 ease activity, prognosis and therapy response.

Methods: We applied Serum Antigen Selection (SAS), an unbiased and high-
throughput antibody profiling procedure based on cDNA phage display. First,
a cDNA phage display library was constructed from synovial hip tissue from 3
axSpA patients and screened for antibody reactivity in pooled plasma of early
axSpA patients (n=10). By performing SAS, we identified antibodies in the axSpA
plasma pool that were reactive against 104 different antigenic targets. These tar-
gets correspond to both known proteins and novel linear peptides. In a first valida-
tion, antibody reactivity against each of these 104 SAS-identified targets was
determined in pooled plasma of additional early axSpA patients (n=50) and
healthy controls (HC, n=30). Antigenic targets that showed highest reactivity in
axSpA plasma pools were further validated in individual plasma samples of early
axSpA patients (n=71) and HC (n=79) using phase enzyme-linked immunosorb-
ent assay (ELISA).

Results: Increased antibody reactivity against 7 targets was found in pooled plasma
of additional early axSpA patients. Further validation of these 7 antigenic
targets in individual plasma samples revealed antibody reactivity in 39% of the
early axSpA patients (28/71) compared with 21% of the HC (15/73). By forming a
biomarker panel with 4 of these targets, specificity could be improved to 88% (9/73
HC) with only a slightly decrease in sensitivity (34%, 24/71).

Conclusions: We identified autoantibody reactivity to novel antigenic targets in
early AS patients. In order to establish the true biomarker potential, antibody reac-
tivity against our identified novel antigenic targets will be further validated in an
independent cohort of axSpA patients, rheumatic controls and low back pain con-
trols. Identification of antibody reactivity against novel antibody targets in early
axSpA patients can contribute to novel biomarkers for an enhanced diagnosis and
might provide more insight into the underlying disease pathology, resulting in
novel treatment strategies and eventually improve disease outcome in axSpA
patients.

REFERENCE:
[1] Quaden D, et al. Autoimmun Rev. 2016 Aug;15(8):820–825.