analysis (PCA) was applied on the BioQC enrichment scores to (i) identify potential clusters of samples and to (ii) identify the gene signatures responsible for the clustering. In addition, associations between cadherin 11 gene expression and gene signatures were tested.

Results In both studies, cadherin 11 was higher expressed in RA patients compared to healthy controls. PCA performed on gene enrichment scores showed RA patients clustered apart from the healthy controls. Moreover, fibroblast, macrophage, lymphocyte and osteoclast gene signatures were significantly enriched in the RA patients compared to healthy controls in both studies. Unexpectedly, an adipokine-related signature was significantly enriched in RA patients from one transcriptomics dataset (GSE77298), while only showing a trend in the second set (GSE7037). In addition, in both studies Cadherin 11 was associated positively with fibroblast and lymphocyte signatures and negatively with adipokine-related signature.

Conclusions The identified cadherin 11 related gene signatures expand our knowledge on cadherin 11 biology in human RA and may serve as potential biomarkers for RA studies in the future.

REFERENCES

Disclosure of interest K. Hatje Employee of: Roche, T. Kam-Thong Employee of: Roche, D. Hartl Employee of: Roche, G. Duchateau-Nguyen Employee of: Roche

PO42 TARGETING NF-kB SIGNALLING IN B CELLS: A POTENTIAL NEW TREATMENT MODALITY FOR ANTIBODY MEDIATED AUTOIMMUNE DISEASES
1. J.P Van Hamburg, 2P. Tijbenburg, 3B. Helder, 4L. van Keep, 1K. Wesenhagen, 3P. Kucharzewka, 2MH Jansen, 1A. Al-Soudi, 1PL Klarenbeek, 1H. Olsson, 2N. de Vries, 2J Kuipers, 3SW Tast, 1Amsterdam Rheumatology and Immunology Centre, Academic Medical Centre University of Amsterdam; 2Department of Experimental Immunology, Academic Medical Centre/University of Amsterdam, Amsterdam, Netherlands; 3Respiratory Inflammation and Autoimmunity IMED Biotech Unit, AstaZeneca, Gothenburg, Sweden

Introduction The pivotal role of B cells in the pathogenesis autoimmune diseases such as ANCA-associated vasculitis (AAV) is well-established and further substantiated by beneficial therapeutic effects of rituximab (anti-CD20 B cell targeted therapy). However, this results in prolonged B cell depletion while long-lived plasma cells are not targeted. Thus there is a need for novel therapeutics targeting cells in the B-cell lineage in AAV. Novel targets might be encountered in the NF-kB signalling pathway, which acts downstream of various B cell surface receptors, including the B cell antigen receptor, CD40, BAFFR and TLRs, and is crucially involved in B cell responses.

Objectives To identify whether inhibition of NF-kB signalling by novel pharmacological inhibitors is effective in targeting B cell responses in general and more specifically blocks (auto) antibody production and plasmablast differentiation in B cells from AAV patients.

Methods PBMC and sorted B cells from AAV patients and healthy donors were cultured with T cell-dependent (anti-IgM +anti CD40+IL-21) and T cell-independent (CpG +IL-2) stimuli. NF-kB signalling was targeted in these cultures by small molecule inhibitors of NF-kB inducing kinase (NIK, non-canonical NF-kB signalling) and IKKβ (canonical NF-kB signalling). Downstream NF-kB signalling and nuclear NF-kB translocation was determined by Western blot and confocal imaging. Effects on B cell proliferation and differentiation were determined by CFSE dilution assays and flow cytometric analysis of B cell markers. (Auto)antibody production was measured by ELISA.

Results In B cells, targeting of NIK and IKKβ effectively inhibited non-canonical or canonical NF-kB signalling, respectively. In a B cell stimulation assay, NIK and IKKβ inhibition significantly reduced T cell-dependent (anti-IgM +anti CD40+IL-21) and T cell-independent (CpG +IL-2) B cell proliferation, plasmablast differentiation (CD27+++/CD38+), and antibody production. The effects of NIK inhibition appeared to be B cell-specific as T cell proliferation was largely unaffected. Currently, studies are ongoing to investigate the effect of IKKβ inhibition on B cell responses and to explore the effects of targeting NF-kB signalling in AAV B cells.

Conclusions These data demonstrate that inhibition of NF-kB signalling in B cells results in the modulation of various B cell responses. Ongoing studies will indicate whether targeting of NF-kB signalling in B cells may be an effective novel treatment modality for AAV.

Disclosure of interest None declared

PO43 INVESTIGATING IL-6 INTRACELLULAR SIGNALLING IN PERIPHERAL BLOOD CELL SUBSETS IN PATIENTS AT EARLY AND LATER STAGES OF RHEUMATOID ARTHRITIS (RA)
1,2L Guboustad*, 1,2L Hunt, 1,2C Wong, 1P Emeby, 1,2M McDermott, 1,2A Aslam, 1,2M Budh, 1Leeds Institute of Rheumatism and Musculoskeletal Medicine, University of Leeds; 2NHRR-Leeds Biomedical Research Centre (NIHR-LEBRC), Leeds Teaching Hospitals NHS Trust, Chapel Allerton Hospital, Leeds, UK

Introduction Rheumatoid arthritis (RA) is a chronic, inflammatory arthritis that evolves along an immunological and inflammatory disease continuum. The era of targeted biological therapies has been transformative; however, a significant unmet need is the effective tailoring of therapy to deliver optimal treatment responses. In addition, the concept of a window of opportunity is well-recognised whereby early commencement of treatment confers improved outcomes compared to delayed treatment. The importance of pro-inflammatory cytokines TNF and IL-6 in particular, is well recognised; but high, homogeneous response in early RA (ERA) compared to later RA remains unexplained.

Objectives The present project focuses on measuring the phosphorylation of STAT3 (p-STAT3) levels as an indication of the activation of IL-6/JAK-STAT signalling pathway at different disease stages (early and established/late). The main aim is to evaluate the variation in cell-subset IL-6 signalling and its association with response to treatment which included IL-6 targeted therapy (Tocilizumab-TCZ) as well as other bDMARD.

Methods Phosphorylation of IL-6/JAK-STAT key transcription factor STAT3 (p-STAT3) was measured using multiparameter phosphoflow cytometry (phosflow) in T-, B- cells and monocytes isolated from peripheral blood of RA patients. Patients cohorts represented groups at different stages of RA: Treatment-naive Early RA (ERA group) n=20. Later RA group...
Objectives We have previously shown that Caucasian rheumatoid arthritis (RA) patients with anti-collagen type II antibodies (anti-CII) have an acute onset phenotype with elevated levels of C-reactive protein (CRP) and erythrocyte sedimentation rate, as well as higher disease activity score and number of swollen joints [Manivel et al. Ann Rheum Dis 2017 September;76(9):1529–1536]. Our aim was to replicate this in a multi-ethnic Malaysian RA cohort.

Methods Anti-CII, anti-CCP2, IgM RF and IgG RF were measured in 1,105 Malaysian early RA patients and 1565 healthy controls of Malay, Chinese or Indian ethnicity in the Malaysian Epidemiological Investigation of RA (MyEIRA) case control study, and related to baseline CRP and to HLA-DRB1* alleles.

Results 106/1,105 (9.6%) of the RA patients had elevated anti-CII. Anti-CII levels were higher in RA patients than in controls (p<0.0001), generally higher in Malay than in Indian or Chinese subjects, and also higher in Malaysian than in Swedish healthy controls. All measured autoantibodies associated with elevated baseline CRP. The occurrence of anti-CII did not associate with the occurrence of anti-CCP2, IgG RF and IgM RF, and when patients with only one antibody were compared to antibody negative patients, only anti-CII associated with elevated CRP (p=0.031). HLA-DRB1*12:01 positive patients has higher levels of anti-CII (p=0.01) whereas Malaysian Malay patients with HLADRBI*12:02 had lower anti-CII levels (p<0.002) as compared to individuals lacking the corresponding genotype.

Conclusions Elevated anti-CII levels at the time of RA onset associate with an early inflammatory RA phenotype not only in Caucasian, but also in an Asian RA population. This supports our hypothesis that the association between early elevations of anti-CII and the acute onset RA phenotype is a finding of global validity.