Background Autoantibodies to citrullinated proteins (ACPA) are specifically associated to rheumatoid arthritis (RA) and produced in the inflamed synovium where citrullinated fibrin, their main antigen, target is abundant. Using a human in vitro model we showed that macrophages generated by differentiation of blood monocytes from healthy individuals or patients with RA secrete TNF-α in response to immune complexes formed by ACPA and citrullinated fibrinogen (ACPA-IC). Moreover while in both healthy individuals and RA patients the TNF-α secretion was found to be highly restricted to RA patients and seem to be characteristic for the SF CD14-positive monocyte-macrophages.

Conclusions These studies will provide new molecular insights into regulatory circuits that control the production of antibodies and could potentially lead to new avenues for diagnosing or treating diseases associated with aberrant plasma cell development, e.g., primary antibody deficiencies, plasma cell malignancies, and autoimmune disorders.

**A5.17 IGG4(+) B-CELL CLONES DOMINATE THE PERIPHERAL BLOOD IN IGG4-ASSOCIATED CHOLANGITIS**

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**Background** IgG4-related disease (IgG4-RD) is a novel disease entity characterised by elevated serum IgG4 levels, IgG4(+) plasmacytic infiltration and fibrosis in various organs. We hypothesised that, if elevated IgG4 titers would be caused by antigen-driven immune responses, clonally expanded, IgG4(+) B cells and plasma cells might be present in affected tissue and peripheral blood.

**Objectives** To analyse the presence of IgG4(+) expanded B-cell clones in peripheral blood (PB) before and after successful therapy of patients with IgG4-associated cholangitis (IAC), and to compare this to healthy and disease controls using a newly developed high throughput sequencing (HTS) protocol for analysis of the B-cell receptor (BCR) repertoire.

**Methods** In 6 IAC patients the BCR repertoire was assessed in PB before and after 4 and 8 weeks of prednisolone (median 40mg, range 20–40 mg) treatment. As controls 6 healthy controls (HC) and 8 ACPA-negative patients with pancreaticobiliary disease were analysed (DC). In two patients a paired duodenal papilla biopsy was obtained at baseline. After isolation of mRNA the BCR_ heavy-chain was amplified, including the CDR3 region, thus fingerprinting unique clones. In our HTS protocol the number of clonal reads can be used as a measure for ‘dominance’; clones with a frequency of >0.5% were considered dominant.

**Results** At baseline, a mean of 15.1% of all clones was IgG(+) in IAC (similar in HC/DC). Among the IAC IgG(+) clones, the most dominant ones were IgG4(+) (mean rank: 1st in IAC versus 65th in HC (p < 0.005) and 55th in DC (p < 0.005)). Across all isotypes in every IAC patient IgG4(+) BCR clones were present among the 10 most dominant BCR clones which was not observed in any of the controls. The papilla contained the same dominant IgG4(+) clones that were detected in the paired blood samples. After 4 and 8 weeks of therapy, the contribution of IgG4(+) clones specifically to the BCR-repertoire was negligible (median 0.19%, IQR 0.16–0.21%), mirroring a sharp decline in serum IgG4 in conjunction with regression of clinical symptoms.

**Conclusions** Our findings indicate that IgG4(+) clones are abundantly present within the repertoire of IAC patients, in contrast to healthy or disease controls. The inflamed tissue was shown to contain the same expanded IgG4(+) clones, suggesting an antigen-driven immune response in IgG4-RD. A possible central role for IgG4(+) B cells is furthermore supported by the finding that IgG4(+) clones in peripheral blood specifically disappear upon successful corticosteroid therapy.