INCB050465 reduced the absolute counts of germinal center (CD19⁺GL7⁺) and marginal zone (CD19⁺CD21⁺) B cell subsets. Anti-dsDNA antibodies were abrogated by INCB050465 therapy ($p < 0.0001$).

Conclusion: INCB050465, a selective PI3K δ inhibitor, was highly efficacious against immune-mediated mechanisms associated with lupus nephritis, but not cutaneous lupus disease manifestations in this preclinical model. Treatment-induced preservation of kidney tissue integrity corresponded to specific B cell subset modulation and autoantibody reduction. Selective PI3K δ inhibitor treatment did not induce lymphocyte depletion.

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THU0215 IGM ANTIBODIES AGAINST MALONDIALDEHYDE AND PHOSPHORYLCHOLINE IN DIFFERENT SYSTEMIC RHEUMATIC DISEASES

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Background: IgM antibodies against phosphorylcholine (anti-PC) and malondialdehyde (anti-MDA) may have protective properties in cardiovascular or rheumatic diseases including SLE and RA.¹⁻⁴ Little is known about their role in other systemic rheumatic conditions.

Objectives: The objective is to compare different rheumatic conditions in relation to these antibodies, and also clinical outcome, with focus on cardiovascular disease. We also aim to characterize them and compare them by use of proteomics.

Methods: IgM anti-PC and anti-MDA was measured using ELISA in patients with SLE (374), RA (354), Mixed connective tissue disease (MCTD, 77), Systemic sclerosis (SSc, 331), Sjögren's syndrome (SjS, 324), primary antiphospholipid syndrome (PAPS, 65), undifferentiated connective tissue disease (UCTD, 118) and 515 matched healthy controls (HC). Cardiovascular score (CV) was broadly defined based on clinical disease symptoms. Anti-PC and anti-MDA peptide/protein characterization were compared using a proteomics de novo sequencing approach. IgM anti-MDA and anti-PC were extracted from total IgM. The proportion of Treg cells was determined by flow cytometry.

Results: The maximal difference between cases and controls was shown for MCTD: significantly lower IgM Anti-PC but not anti-MDA among patients (median 49.3RU/ml vs 70.4 in healthy controls, $p(t\text{-test})=0.0037$). Low levels (below 25th percentile) of anti-PC but not anti-MDA were significantly more prevalent in MCTD, SLE, SjS and SSc. The IgM anti-PC variable region profiles were distinctly different and also more homologous in their content than anti-MDA. Anti-PC but not anti-MDA were significantly negatively correlated with CV in the whole patient group. In contrast to IgM anti-PC, IgM anti-MDA did not promote polarization of Tregs.

Conclusion: Anti-PC could be a protection marker for MCTD and also for SLE, SjS and SSc while anti-MDA did not differ. anti-PC level is negatively correlated with CV in the patient group cohort. These findings could have both diagnostic and therapeutic implications, one possibility being active or passive immunization with PC.

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THU0216 IGG1 ANTIBODIES AGAINST PHOSPHORYLCHOLINE ARE ASSOCIATED WITH PROTECTION IN SLE AND ATHEROSCLEROSIS: POTENTIAL UNDERLYING MECHANISMS

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Background: IgM antibodies against phosphorylcholine (anti-PC) may be protective in atherosclerosis, cardiovascular disease (CVD) and systemic lupus erythematosus (SLE). Less is known about other anti-PC isotypes and subclasses. In this study, we study the role of IgG1 and IgG2 anti-PC, with focus on atherosclerosis and SLE.

Objectives: To study the role of IgG1 and IgG2 anti-PC, with focus on atherosclerosis and SLE, both in a clinical setting and by experimental studies, where we use our in-house produced monoclonal IgG1 anti-PC.

Methods: We determined IgG1 and IgG2 anti-PC in our SLE cohort study (SLEVIC), among 116 SLE-patients from Karolinska University Hospital Huddinge and 110 population controls matched for age and gender. The level of antibodies was measured by ELISA. For functional studies, we used three of our in-house generated, fully human monoclonal IgG1 anti-PC (A01, D05, E01). Primary human macrophages were derived from peripheral blood. Apoptosis was induced in Jurkat T-cells and pre-incubated with A01, D05, E01 or isotype control IgG1 and effect on phagocytosis by macrophages studied. Anti-PC peptide/protein characterization was determined in anti-PC clones compared to isotype control using a proteomics de novo sequencing approach.

Results: IgG1 but not IgG2 anti-PC levels were higher among SLE patients than controls ($p=0.02$). IgG1 anti-PC was negatively associated with prevalence of atherosclerotic plaques, below 10th percentile, (OR: 2.48, CI: 0.69-9.00). IgG1 Anti-PC was negatively associated with CVD, SLICC and SLEDAI (OR: 4.74 CI: 1.29-17.39, OR: 2.978 CI: 0.876-10.098, OR: 5.108 CI 1.3 20.067 respectively). Monoclonal D05 had maximum effect on macrophage efferocytosis efficiency, followed by A01 and E01. This is because anti-PC IgG1s bind to phosphorylcholine exposed on apoptotic cells and facilitate the uptake by macrophage. The in-house produced monoclonal antibodies showed differential binding specificity to PC and PC associated neo-epitopes. Peptide analysis showed difference in the CDR3 region of the three anti-PC IgG1 clones which are crucial for recognition of the phosphorylcholine on the apoptotic cell surface and other neo-epitopes.