and CD138+ B cells in the SMG tissues and the spleen collected from treated group and control group. (means±SD; n=7 per group; * P<0.05, ** P<0.01, *** P<0.001).

**Figure 3.** The proinflammatory cytokine levels of TNF-α, IL-17, and IL-6 in the serum samples from the treated and control group. (means±SD; n=7 per group; * P<0.05, ** P<0.01, *** P<0.001).

**Conclusion:** Leflunomide may prevent and improve salivary gland hypofunction and inhibit immune activation in NOD mice, providing a theoretical basis for evaluating leflunomide in the treatment of Sjögren’s syndrome.

**References:**

DOI: 10.1136/ard.2006.060905.

Acknowledgments: The authors thank the Center for Scientific Research of Aráucano Medical University for valuable help in our experiment.

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2020-eular.2215

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**THU0230**

IGG ANTIBODIES AGAINST PHOSPHORYLCHOLINE ARE NEGATIVELY ASSOCIATED WITH DISEASE ACTIVITY, DISEASE DAMAGE, CARDIOVASCULAR DISEASE AND ATHEROSCLEROSIS IN SLE: POTENTIAL UNDERLYING MECHANISMS.

D. Thiggarajan1, R. Fiskesund1, J. Steen1, M. Rahman1, S. Lundström1, J. Frostegård1.

1Karolinska Institutet, Stockholm, Sweden

**Background:** Phosphorylcholine (PC) is an important component in cellular membranes and in lipoproteins that is exposed and recognized by the immune system, when cells undergo apoptosis or lipoproteins like LDL undergo oxidation. PC is also exposed in some microorganisms including nematodes and bacteria (non-self). We reported that IgM anti-PC is associated with protection in atherosclerosis, SLE, RA and other chronic inflammatory conditions. We also reported potential underlying protective mechanisms: 1: increase in clearance of human dead cells, 2: inhibition of uptake of oxLDL in macrophages, 3: inhibition of cell death, 4: anti-inflammatory; 5: promotion of polarization of T regulatory cells in SLE-patients' T cells from SS-patients.

**Objectives:** We here study IgG1 and IgG2 anti-PC, with focus on atherosclerosis and SLE and properties of fully human IgG1 clones, in relation to SLE.

**Methods:** We determined anti-PC by ELISA in 116 SLE-patients and 110 age- and sex-matched controls. For functional studies, we used three in-house generated, fully human monoclonal IgG1 anti-PC (A01, D05, E01). Apoptosis was induced in Jurkat T-cells and pre-incubated with A01, D05, E01 or isotype control and effects on effecotirocyte human macrophages studied. Anti-PC peptide/protein characterization was determined using a proteomics de novo sequencing approach.

**Results:** IgG1 but not IgG2 anti-PC levels were higher among SLE patients (p=0.02), IgG1 anti-PC was negatively associated with SLICC and SLEDAI (OR: 2.978 CI: 0.876-10.098, OR: 5.108 CI 1.320.067 respectively) and negatively associated with CVD, atherosclerotic plaques and echolucent (potentially vulnerable plaques) but the association for the two former was not significant after controlling for confounders. D05 had maximum effect on macrophage effecotirocyte efficiency, followed by A01 and E01. The 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 PC on apoptotic cell surface and other neo-epitopes.

**Conclusions:** Anti-PC IgG1 is negatively associated with disease activity, and disease damage in SLE, but the negative association with CVD is also dependent on confounding risk factors. One potential underlying mechanism could be increased clearance of dead cells.

**References:**


Disclosure of Interests: : Divya Thigarahajan: None declared, Roland Fiskesund: None declared, Johanna Steen: None declared, Mizanur Rahman: None declared, Susanna Lundström: None declared, Johan Frostegård: Consultant of: Abbvie, Astellas, Asahi-kasei, Astellas, Mitsubishi-Tanabe, Chugai, Takeda, Sanofi, Bristol-Myers, and Pfizer, Y amagata Kaoru: None declared, Naoaki Ohkubo: None declared, He Hao: None declared, Shingo Nakayamada Grant/

THU0231

IL-2 DRIVES THE CONVERSION OF T FOLLICULAR HELPER TO T FOLLICULAR REGULATORY CELLS THROUGH EPIGENETIC MODIFICATION IN SYSTEMIC LUPUS ERYTHEMATOSUS

H. Hao1,2, S. Nakayamada1, Y. Kaoru1, N. Oikubo1, S. Iwata1, Y. Tanaka1. 1University of Occupational and Environmental Health, School of Medicine, First Department of Internal Medicine, Kitakyushu, Japan; 2The Fourth Hospital of Hebei Medical University, Department of Immuno-Oncology, Shijiazhuang, China

Background: Systemic lupus erythematosus (SLE) is a complex polygenic autoimmune disease characterized by immune-system aberrations. Among several types of immune cells, T follicular helper (Tfh) cells promote autoantibody production, whereas T follicular regulatory (Tfr) cells suppress Tfh-mediated antibody responses. (1)

Objectives: To identify the characteristics of Tfr cells and to elucidate the mechanisms of conversion of Tfh cells to Tfr cells, we probed the phenotype of T helper cells in patients with SLE and underlying epigenetic modifications by cytokine-induced signal transducer and activators of transcription (STAT) family factors.

Methods: Peripheral blood mononuclear cells from SLE patients (n=44) and healthy donors (HD; n=26) were analyzed by flow cytometry. Memory Tfh cells were sorted and cultured under stimulation with T cell receptor and various cytokines. Expression of characteristic markers and phosphorylation of STATs (p-STATs) were analyzed by flow cytometry and quantitation PCR. Histone modifications were evaluated by chromatin immunoprecipitation.

Results: The proportion of CXCR5+FoxP3+ Tfr cells in CD4+ T cells tended to increase (2.1% vs 1.7%, p<0.10) in SLE compared to HD. The percentage of PD-1+ activated Tfh cells was significantly higher in SLE compared to HD (17.5% vs 5.9%, p<0.01). Furthermore, active patients had a higher ratio of activated Tfh/Tfr compared to inactive patients. In vitro study showed that IL-2, but not other cytokines such as IFN-γ, IL-10, IL-21, and IL-27, induced the conversion of memory Tfh cells to functional Tfr cells characterized by CXCR5+β-catenin+FoxP3+3pSTAT5+ pSTAT5+ Tfh cells. The loci of FOXP3 at STAT binding sites were marked by bivalent histone modifications. After IL-2 stimulation, STAT5 directly bound on FOXP3 gene loci accompanied by suppressing H3K27me3. Finally, we found that serum level of IL-2 was decreased in SLE and that stimulation with IL-2 suppressed the generation of CD38+CD27+B cells by ex vivo coculture assay using Tfh cells and B cells isolated from human blood.

Conclusion: Our findings indicated that the regulatory function of Tfr cells is impaired due to the low ability of IL-2 production and that IL-2 restores the function of Tfr cells through conversion of Tfh cells to Tfr cells in SLE. Thus, the reestablishment of the balance between Tfh and Tfr cells will provide important therapeutic approaches for SLE.

References:


Disclosure of Interests: : He Hao: None declared, Shingo Nakayamada Grant/ research support from: Mitsubishi-Tanabe, Takebe, Novartis and MSD, Speakers bureau: Bristol-Myers-Sanofi, AbbVie, Eisai, Eli Lilly, Chugai, Asahi-kasei and Pfizer, Yamagata Kaoru: None declared, Naoaki Ohkubo: None declared, Shingo Nakayamada Grant/