Background: Rheumatoid arthritis (RA) has been associated with increased cardiovascular (CV) risk and metabolic changes. Objectives: We wished to determine how the Janus kinase (JAK) inhibitor tofacitinib influences vascular pathophysiology and metabolites of the arginine and methionine-homocysteine pathways. Methods: Thirty RA patients with active disease were treated with either 5 mg or 10 mg bid tofacitinib and evaluated at baseline and after 6 and 12 months. We determined DAS28, CRP, IgM rheumatoid factor (RF) and anti-cyclic citrullinated peptide (aCCP) levels. We assessed brachial artery flow-mediated vasodilation (FMD), carotid intima-media thickness (IMT) and pulse-wave velocity (PWV) by ultrasound. We also determined plasma L-arginine, L-citrulline, L-ornithine, inducible nitric oxide synthase (iNOS), asymmetric (ADMA) and symmetric dimethylarginine (SDMA), L-N-nomonomethyl-arginine (LN-NMMA), cysteine, homocysteine, and methionine levels. Results: Twenty-six patients completed the study. Tofacitinib treatment maintained FMD and PWV. Ten mg bid tofacitinib significantly increased L-arginine, L-ornithine, iNOS and methionine levels after 12 months. Tofacitinib transiently increased L-citrulline and LN-NMMA and decreased homocysteine levels after 12 months. Based on L-citrulline, L-ornithine, ADMA and SDMA levels, L-arginine remained highly available for endothelial NO production. Multivariate analysis indicated variable correlations of L-arginine, L-citrulline, ADMA, LN-NMMA, homocysteine and methionine with DAS28, CRP, ESR and RF but not with aCCP. Regarding vascular pathophysiology, only PWV and methionine correlated with each other after 12 months. Conclusion: Tofacitinib suppressed systemic inflammation in RA yielding stabilization of vascular function. It may exert CV protective effects in RA, at least in part, by shifting L-arginine metabolism to high arginine availability and decreasing homocysteine levels.

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POS0384

A NOVEL MECHANISM LINKING MUCOSAL BACTERIA WITH AUTOANTIBODY RESPONSES IN RA: ACETYLATED BACTERIAL LYSATE AS A MODEL ANTIGEN

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Background: Rheumatoid arthritis (RA) is characterized by autoantibodies against post-translationally modified proteins (AMPA) such as citrullinated, carbamylated and acetylated proteins. Importantly, these antibodies are highly cross-reactive AMPA responses in mice and they are recognized by human AMPA. This suggests that acetylated bacterial proteins could possibly be involved in the breach of tolerance in RA.

Methods: Acetylated bacterial proteins are potent antigens that can induce cross-reactive AMPA responses in mice and they are recognized by human AMPA. We wished to determine whether acetylated proteins of bacterial origin (1) are recognized by human-derived AMPA and AMPA expressing B cells; and (2) can induce AMPA development when used to immunize mice.

Results: Repetitive immunization of mice with EABP resulted in an AMPA response recognizing acetylated, carbamylated and citrullinated proteins. AMPA titers in these mice exceeded the titers in the positive control mice immunized with AcOVA and were substantially higher than in the NABP-immunized mice (Figure 1B). Human-derived monoclonal AMPA recognized EABP and IABP (not shown). B cell activation (measured by Syk phosphorylation) assay indicated that AMPA expressing B cells recognized EABP and (to a lesser extent) IABP, but not NABP (Figure 1C).

Conclusion: Acetylated bacterial proteins are potent antigens that can induce cross-reactive AMPA responses in mice and they are recognized by human AMPA. This suggests that acetylated bacterial proteins could possibly be involved in the breach of tolerance in RA.

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POS0385

DURING DEVELOPMENT OF RHEUMATOID ARTHRITIS, INTERMETATERSAL BURSITIS MAY OCCUR BEFORE CLINICAL JOINT SWELLING: A LARGE MRI STUDY IN PATIENTS WITH CLINICALLY SUSPECT ARTHRALGIA

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Background: Inflammation of the synovial lining is a hallmark of rheumatoid arthritis (RA). A synovial lining is not only present at synovial joints and tendon sheaths but also at bursae. Inflammation of the synovium-lined intermetatarsal bursae in the forefoot, intermetatarsal bursitis (IMB), was recently identified with MRI. It is specific for early RA and present in the majority of RA patients at diagnosis. During development of RA, MRI-detectable subclinical synovitis and tenosynovitis often occur before clinical arthritis presents. Whether IMB is also present in a pre-arthritis stage is unknown.

Objectives: To assess the occurrence of IMB in patients with clinically suspect arthralgia (CSA) and its association with progression to clinical arthritis in a large MRI-study.

Methods: We studied 524 consecutive patients presenting with CSA. CSA was defined as recent-onset arthralgia of small joints that is likely to progress to RA based on the clinical expertise of the rheumatologist. Participants underwent unilateral contrast-enhanced 1.5T MRI of the forefoot, metacarpophalangeal (MCP) joints and wrist at baseline. Thereafter patients were followed for detection of clinical arthritis, as identified at physical joint examination by the rheumatologist. Baseline MRIs were evaluated for IMB at all 4 intermetatarsal spaces. Also synovitis, tenosynovitis and osteitis were
Cross-boosting and skewing of AMPA responses in immunized mice

**A**

**Anti-AcFb response**

**B**

**AMPA reactivity profile evolution in different mouse strains**

**Discussion of Interests:** None declared

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### POS0387

**ACPA STATUS CORRELATES WITH DIFFERENTIAL IMMUNE PROFILE OF RHEUMATOID ARTHRITIS PATIENTS**

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**Background:** Rheumatoid arthritis (RA) is a progressive erosive autoimmune disease that affects 1% of the world population. Anti-citrullinated protein autoantibodies (ACPA) are routinely used for the diagnosis of RA, however 20-30% of patients are ACPA negative. ACPA status is a delineator of RA disease endotypes with similar clinical manifestation but potentially different pathophysiology. Elucidating the underlying mechanisms of disease pathogenesis could inform a treat to target approach for both ACPA-positive and ACPA-negative RA patients.

**Objectives:** To identify peripheral blood and synovial tissue immune population differences that correlate with ACPA disease endotype.

**Methods:** Detailed high dimensionality flow cytometric analysis with supervised and unsupervised algorithm analysis of ACPApos and ACPAneg RA patient peripheral blood and synovial tissue single cell suspensions. Ex vivo peripheral blood and synovial tissue T cell stimulation and cytokine production characterization. RNAseq analysis with specific pathway enrichment analysis of ACPApos and ACPAneg RA patient synovial tissue biopsies.

**Results:** Detailed profiling based on high dimensionality flow cytometric analysis of key peripheral blood and synovial tissue immune populations including B, T follicular helper (Tfh) cells, T peripheral helper cells (Tph) and CD4 T cell proinflammatory cytokine responses with supervised and unsupervised algorithm analysis revealed unique RA patient peripheral blood B cell and Tfh cell profiles. ACPApas RA patients were characterised by significantly (*P=0.03) increased frequency of Th (CXCR5+CD4+) cells and distinct clustering influenced by increased switched (IgG2D27) and DN (IgD2D27) memory B cells compared to ACPAneg RA patients. Surprisingly synovial tissue B cell subpopulation distribution was similar between ACPAneg and ACPApas RA patients, with significant accumulation of switched and double negative memory B cells, highlighting a key role for specific B cell subsets in both disease endotypes. Interestingly, synovial tissue CD4 T cell...