SAT0060

CHOLESTEROL SEQUESTERING IN MACROPHAGES CONTRIBUTES TO THE LIPID PARADOX IN CHRONIC ARTHRITIS

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Background: Patients with active rheumatoid arthritis (RA) have increased cardiovascular mortality, paradoxically associated with reduced circulating lipid levels (1-3). Several disease-modifying antirheumatic drugs (DMARDs), such as the JAK inhibitor tofacitinib, ameliorate disease activity along with an increase in serum lipids (4, 5). We previously demonstrated *in vitro* that tofacitinib favored cholesterol efflux from macrophages through an ABCA1-dependent mechanism (6). Furthermore, tofacitinib-treated chronic arthritic rabbits showed increased circulating lipids and decreased lipid accumulation within the synovium (6).

Objectives: Our aim was to explore *in vivo* whether inflammation impedes cholesterol efflux from macrophages, and whether tofacitinib restores macrophage cholesterol release during chronic arthritis. For that purpose, we assessed the ability of intraperitoneally-injected ³H-cholesterol labelled macrophages to efflux cholesterol to circulating lipoproteins in collagen-induced arthritis (CIA) mice treated with tofacitinib or placebo, as compared to healthy controls.

Methods: DBA/1J mice were randomly assigned to healthy controls (Control, n = 9), CIA (CIA, n = 6) and CIA mice receiving 50 mg/kg/day tofacitinib, orally, for three consecutive days, starting on day 39 after CIA induction and coinciding with disease peak (CIA+TOFA, n = 6). The day after, ³H-cholesterol labeled RAW264.7 macrophages were intraperitoneally injected into mice and tracer appearance was monitored in plasma lipoprotein subfractions, synovium, liver, bile and feces.

Results: The CIA group showed higher C-Reactive protein levels (CRP, µg/ml; Control: 10.90±0.49, CIA: 13.86±1.05, p=0.03 vs. Control) and lower circulating ³H-cholesterol levels (% of injected disintegrations per minute (dpm)/ml; Control: 1.29±0.11, CIA: 0.92±0.11, p=0.04 vs. Control). Both serum CRP and ³H-cholesterol –particularly the HDL fraction– were restored to baseline after the treatment with the JAK inhibitor (CIA +TOFA: 10.97±0.67 µg/ml and 1.37±0.20 % of injected dpm/ml, respectively, p=0.05 vs. CIA). Concomitantly, we observed an upward trend in ³H-cholesterol accumulation within the synovium of CIA animals as compared to controls, which tended to normalize with the treatment.

Conclusion: Systemic inflammation induces cholesterol sequestering within macrophages *in vivo* by acting on cholesterol efflux transporters (6). Tofacitinib favors cholesterol release to plasma lipoproteins, hence increasing circulating cholesterol. This is not only due to a decrease in inflammation –an effect very likely shared with some other biologic DMARDs–, but also to a direct mechanism on ABCA1 transporters that favors cholesterol efflux. To our knowledge, this is the first report suggesting that cholesterol dynamics in the macrophage may contribute to the overall circulating cholesterol levels, especially considering that this phenomenon may occur in other cell types, such as adipocytes.

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SAT0061

IMPORTANT ROLE OF CD11C+ CELLS IN INFLAMMATORY ARTHRITIS

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Background: Dendritic cells (DCs) are important antigen presenting cells (APCs) and therefore they play an important role in bridging the innate and the adaptive immune response. DCs can be divided in different subsets with specific functions. As powerful APCs, DCs are thought to play an important role in the induction of autoimmune diseases such as

rheumatoid arthritis. However, the active role of DCs in joint inflammation is not known yet.

Objectives: Investigation of the role of DCs cells in joint inflammation and destruction.

Methods: We analyzed histological sections of K/BxN serum transfer arthritis as well as hTNFg arthritis for the presence of CD11c+ cells by immunohistochemistry. We used CD11c-diphtheria toxin receptor (DTR) transgenic mice. K/BxN serum transfer arthritis was induced, and mice were given either DT or PBS or in wt and BARF3 deficient mice. In addition CD11c DTR mice were crossed into hTNFg animals and also received either DT or PBS. The severity of arthritis was determined clinically and histologically.

Results: Both CD8+CD11c+ and CD11b+CD11c+, can be found in synovial tissue in TNF driven arthritis. Upon depletion of CD11c+ cells clinical signs of K/BxN serum transfer arthritis were significantly reduced. Histological analysis found reduced synovial inflammation after the depletion of CD11c+ cells in K/BxN arthritis. In addition, local bone destruction and the number of osteoclasts was also significantly reduced. In addition to K/BxN arthritis, we found that also in TNF-driven arthritis depletion of CD11c+ cells led to a striking reduction of synovial inflammation and a complete depletion of osteoclasts.

Conclusion: These data show that in addition to initiating an adaptive immune response, CD11c+ dendritic cells, are also involved in innate effector mechanisms of inflammatory arthritis. Especially CD11b+CD11c+ and monocyte derived inflammatory seem to play a role in inflammatory arthritis, suggesting that they could be an important therapeutic target.

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SAT0062

STRATIFIED MEDICINE FOR RHEUMATOID ARTHRITIS: PREDICTING RESPONSE TO BIOLOGIC THERAPY USING IMMUNE CELL SIGNATURES

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Background: Treatment selection of biologic therapy for patients with rheumatoid arthritis (RA) is currently a trial and error process, with approximately 40% failing to respond well to the first biologic. The lack of biomarkers to predict treatment response leads to further pain, joint damage, patient anxiety and is cost ineffective for those who are non-responders.

Objectives: We aim to identify immune signatures from a pre-treatment blood test to inform the choice of treatment strategies for stratified medicine.

Methods: RA patients with active disease (DAS28 > 5.1) who failed to respond to conventional DMARDs and were due to commence biologic treatment were included in the BRAGGS cohort. Peripheral blood mononuclear cells (PBMCs) taken before the initiation of biologic treatment were available for 300 patients (good (60%), moderate (25%), and non-

responders (15%) to various biologics (anti-TNFs (68%), Rituximab (16%), Tocilizumab (13%), Abatacept (3%)). PBMCs were left unstimulated or stimulated (anti-CD3/CD28 beads or 10 ng/mL LPS) and stained with three flow cytometry panels including specific surface, intracellular and intranuclear markers to deeply characterise the function of several subsets of monocytes, NK cells, T cells and B cells (e.g. disease-associated cell populations such as PD-1^{hi}CXCR5⁺ peripheral T helpers (Rao DA *Nature* 2017), CD27⁺HLA-DR⁺ effector CD4⁺ T cells (Fonseka CY *Sci Transl Med* 2018) and cytotoxic PD-1⁺CXCR5⁺ CD8⁺ T cell subsets, Tbet⁺CD11c⁺ autoimmune-associated B cells, CD14⁺IL1β⁺ pro-inflammatory monocytes (Zhang F *BioRxiv* 2018)). Hypothesis-free clustering algorithms were also used for data analysis to identify unreported cell populations. Statistical association testing was performed using mixed effects ordinal (EULAR response) or linear (DAS28 or its components) regression models.

Results: Preliminary interim analysis identified associations between pan-biologic non-response and spontaneous expression of pro-inflammatory cytokines (Th1, Th17 lineage) by CD4⁺ T cells ($p < 0.003$). Good response to all biologic drugs was independently associated with the number of CD56^{dim}CD16⁺ NK cells ($p < 0.001$). Good response to anti-TNFs was associated with TNFα, IFNγ and perforin producing CD4⁺ T cells after *in vitro* stimulation with anti-CD3/CD28 ($p < 0.02$).

Conclusion: Ongoing work involves the replication of these results. The identification of immune cell types associated with response to a particular class of biologic drugs (e.g. anti-TNFs, but not other classes) might inform the choice of first line biologic drugs based on individual patients' immune profiles (stratification to treatment response categories). Cells or cytokines generally associated with non-response to all biologics could represent new therapeutic targets, at least in some patients groups.

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SAT0063

ASSOCIATION OF SMOKING WITH TRIPLE CONCORDANT SEROPOSITIVITY IN RA PATIENTS, AND WITH RHEUMATOID FACTOR IN THE REMAINING PATIENTS

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Background: The contribution of cigarette smoking to the risk of rheumatoid arthritis (RA) is larger for seropositive than for seronegative patients. Current pathogenic models explain this difference via the production of anti-citrullinated protein antibodies (ACPA) induced by protein citrullination in the lungs as a consequence of smoking. However, there are inconsistent results with this model including the van Wesemael *et al.* report, which found an association of smoking with the concurrent presence of ACPA, rheumatoid factor (RF) and anti-carbamylated protein antibodies (ACarPA), rather than with ACPA.

Objectives: We aimed to explore the relationship between smoking and the presence of FR, ACPA and ACaPA and their combinations in patients with RA.

Methods: Six cohorts with 2253 RA patients were obtained to replicate the van Wesemael *et al.* results. After replication, they were combined

with the three cohorts from that study comprising 2238 patients to a total of 4491 patients. The results from the different cohorts were combined by fixed-effects meta-analysis. Most analyses involved comparisons between two levels of smoking exposure, never and ever smokers, considering the RF/ACPA/ACaP patients as the reference.

Results: Analysis of the replication set confirmed the predominant association of smoking with the concurrent presence of the three RA autoantibodies (OR = 1.99, $P = 2.5 \times 10^{-6}$), whereas the patients with one or two antibodies were not different from the patients without antibodies (OR = 1.22, $p = 0.4$ and OR = 1.22, $p = 0.3$, respectively). The combined meta-analysis with all the cohorts clarified the dominant association of smoking with the triple concordant seropositivity (OR = 2.00, $p = 4.4 \times 10^{-16}$). In contrast, there was no association with the patient bearing one autoantibody (OR = 1.12, $p = 0.4$), and an in-between association with the concurrent presence of two antibodies (OR = 1.26, $p = 0.009$). Moreover, the association with the presence of three antibodies was significantly larger than with two antibodies (OR = 1.54, $p = 1.4 \times 10^{-6}$), whereas the association with the presence of two antibodies was not larger than with one autoantibody (OR = 1.11, $p = 0.3$). In the patients remaining after exclusion of the triple seropositive, the smokers were exclusively associated with the RF⁺ (OR = 1.28, $p = 0.03$ and OR = 1.30, $p = 0.004$ in the double and single positive patients, respectively). This association was independent of the reference, either the triple seronegative (OR = 1.29, $p = 0.001$) or all the RF⁺ patients (OR = 1.32, $p = 0.0002$).

Conclusion: Smoking increases RA susceptibility by promoting pathways leading to the concurrent presence of the three RA autoantibodies and, in its defect, to the production of RF. These actions are not covered by current pathogenic models and suggest that smoking accelerates epitope spreading.

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SAT0064

EXPANSION OF CD16+ MONOCYTE SUBSETS AND ACE EXPRESSION ARE ASSOCIATED WITH ARTERIAL THICKENING AND VASCULAR FUNCTION IN VERY EARLY RHEUMATOID ARTHRITIS

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Background: monocytes are largely recognized as drivers of the atherosclerosis development, the leading determinant of cardiovascular (CV) morbidity in rheumatoid arthritis (RA). Far from being a unique population, functionally and phenotypically subpopulations can be distinguished, although their relevance to CV disease is uncertain. Recently, the expression of angiotensin-converting enzyme (ACE) expression has been