Results: Our results demonstrate that early exposure to S100A8 interferes with *in-vitro* differentiation of moDCs. Compared to controls S100A8-exposed moDCs show dramatically reduced surface expression of co-stimulatory molecules upon LPS-induced maturation. In addition, early treatment of moDCs with S100A8 alters the secretion of immune-regulatory cytokines and chemokines depending on the developmental state of moDCs. S100A8-induced effects on moDC maturation are not limited to TLR4 stimulation but rather trigger a common state of unresponsiveness. Furthermore, mitochondrial respiration and glycolytic function is diminished in S100A8-treated moDCs.

As a consequence, S100A8-exposed moDCs have a reduced potential to induce autologous T-cell proliferation. We can show that these differences are mainly caused by reduced surface expression of co-stimulatory molecules on S100A8-treated moDCs.

Mechanistically, genome-wide gene expression analysis reveals dramatic differences in gene expression between S100A8-exposed and conventionally differentiated moDCs. We demonstrate that S100A8 pre-treatment of moDCs significantly blocks LPS-induced gene expression during moDC activation. Interestingly, *in-silico* analysis of transcription factor networks predicts NFκB and C/EBPδ as master regulators of S100A8-induced effects in developing moDCs. C/EBPδ on protein level, indeed, shows reduced expression in S100A8-differentiated moDCs prior and after LPS-induced maturation when compared to conventionally differentiated moDCs.

Conclusions: Taken together, our results demonstrate a novel regulatory mechanism of innate immunity to prevent overwhelming immune responses. Dysregulated repression of detrimental adaptive immune responses might very well contribute to the disease phenotype in auto-immune disorders with high systemic S100A8/A9 levels. Therefore, S100A8-differentiated immune-suppressive DCs potentially represent a promising therapeutic tool to treat auto-immune diseases in the future.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2017-eular.4960

OP0092 INTERLEUKIN 37 REVERSES THE METABOLIC COST OF INFLAMMATION, INCREASES OXIDATIVE RESPIRATION AND IMPROVES EXERCISE TOLERANCE

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Background: The IL-1 family cytokine interleukin 37 (IL-37) has broad anti-inflammatory effects and functions as a natural suppressor of innate inflammation and acquired immunity (1). We have reported that administration of recombinant human IL-37 to wild type mice or expression in mice transgenic for human IL-37 suppress proinflammatory cytokines and curb excessive inflammation in various conditions including inflammatory arthritis (2). Besides these anti-inflammatory effects, IL-37 also induces complex effects on metabolism. In particular, IL-37 can directly activate AMP-activated protein kinase (AMPK), a central regulator of cellular energy homeostasis and exercise-regulated metabolism (3).

Objectives: In this study, we evaluate the effects of IL-37 treatment on exercise tolerance in mice with systemic inflammation induced by LPS injection. We further investigate the effects of IL-37 on exercise tolerance in healthy mice, with specific focus on the metabolic changes induced by IL-37 administration and possibly responsible for a reduction in the metabolic costs of inflammation.

Results: Exogenous administration of IL-37 to healthy mice, not subjected to an inflammatory challenge, also improved exercise performance by 82% compared to vehicle-treated mice (p=0.01). Treatment with 8 daily doses of IL-37 resulted in a further 326% increase in endurance running time compared to the performance level of mice receiving vehicle (p=0.001). These properties required the engagement of the IL-1 decoy receptor 8 (IL-1R8) and the activation of AMP-activated protein kinase (AMPK), since both inhibition of AMPK and IL-1R8 deficiency abrogated the positive effects of IL-37 on exercise performance. Mechanistically, treatment with IL-37 induced marked metabolic changes with higher levels of muscle AMPK, greater rates of oxygen consumption and increased oxidative phosphorylation. Metabolomic analyses of plasma and muscles of mice treated with IL-37 revealed an increase in AMP/ATP ratio, reduced levels of pro-inflammatory mediator succinate and oxidative stress-related metabolites as well as changes in amino acid and purine metabolism.

Conclusions: These effects of IL-37 to limit the metabolic costs of chronic inflammation and to foster exercise tolerance provide a rationale for therapeutic use of IL-37 in the treatment of inflammation-mediated fatigue.

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Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2017-eular.1789

OP0093 IL-38 OVEREXPRESSION INDUCES ANTI-INFLAMMATORY EFFECTS IN MICE ARTHRITIS MODELS AND IN HUMAN MACROPHAGES IN VITRO

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Background: IL-38 is a newly characterized cytokine that belongs to the IL-1 family. This cytokine is expressed in the rheumatoid arthritis (RA) synovial tissue (1) and IL-38 deficient mice have exacerbated arthritis (2).

Objectives: This work aims to analyze the effect of IL-38 overexpression in the joints of arthritic mice, in human macrophages and synovial fibroblasts *in vitro*.

Methods: Articular injections of an adeno-associated virus (AAV2/8) encoding IL-38 were performed in Collagen-Induced Arthritis (CIA), K/BxN Serum Transfer-Induced Arthritis (STIA) and Antigen-Induced Arthritis (AIA) in mice. The effect of IL-38 overexpression was evaluated through clinical scores, immunohistochemistry, microCT, Luminex and RT-qPCR analysis. THP-1 monocytes/macrophages were transduced with a lentiviral vector to overexpress IL-38. Effect of conditioned media from these transduced THP-1 cells was also tested on primary culture: M1 macrophages and fibroblast-like synoviocytes from RA patients (RA-FLS).

Results: Clinical inflammatory scores were significantly decreased after AAV IL-38 injection in joints of mice with CIA and STIA, but not AIA. This decrease was accompanied by reduced macrophage infiltration and a decreased expression of Th17 expressed cytokines (IL-17, IL-23, IL-22, TNFα). However, IL-38 overexpression had no effect on cartilage or bone destruction. *In vitro*, the THP-1 monocytic cell line expressed less IL-6, TNFα and IL-23 after IL-38 overexpression. Conditioned media from these cells, containing released IL-38, was also able to exert an anti-inflammatory effect on human primary M1 macrophages and RA-FLS by reducing their IL-23 (M1) and IL-6 (M1 and RA-FLS) expression.

Conclusions: This study shows for the first time that IL-38 overexpression attenuates the severity of experimental arthritis in two mice arthritis models. IL-38 may exert its anti-inflammatory effects by decreasing the production of pro-inflammatory cytokines by macrophages and synovial fibroblasts. This effect can lead to the development of novel treatment strategies in arthritis.

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Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2017-eular.2257

OP0094 DEVELOPMENT OF A 37-CHANNEL MASS CYTOMETRY (CYTOF) PANEL TO PREDICT TREATMENT RESPONSE IN RHEUMATOID ARTHRITIS

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Background: It is well-established that reducing the inflammation of rheumatoid arthritis (RA) early leads to improved patient outcomes. Patients who fail to respond to conventional DMARDs move on to biologic drugs, however 30% will fail to respond to the first drug tried. Biologics are trialled for at least 3 months before their efficacy can be assessed, during which time irreversible joint damage may occur.

Currently there is no way to predict which drug will be effective in individual patients. It is therefore a research priority to develop a method to predict response to each class of biologic drug. I hypothesise that the immune phenotype of a patient will influence treatment response.

Objectives: This study aims to immunophenotype T cells using mass cytometry and to test novel unbiased methods of analysing high-dimensional data.

Methods: Ten healthy controls (HC) and 10 RA patients with established disease were included. T cells were isolated and stimulated for 4 hours using anti-CD3/anti-CD28 beads in the presence of monensin and brefeldin A. Cells were stained with a 37-channel mass cytometry panel including surface markers, intracellular antigens and transcription factors.

Analysis was performed by conventional biaxial gating alongside tools available on the MRC Cytobank platform, namely Visual t-distributed stochastic neighbour embedding (viSNE), and Cluster identification, characterization, and regression (CITRUS). The CITRUS analysis compared stimulated HC with RA T cells. To