Figure 1: FTS therapy reduces the levels of pathogenic autoantibody and alters glycosylation of autoantibodies.

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SAT0045

A NOVEL SMALL MOLECULE, MBS2133, MODULATES OSTEOCLAST PRE-CURSOR METABOLISM TO INHIBIT OSTEOCLAST DIFFERENTIATION: AN ALTERNATIVE THERAPY FOR OSTEOLYTIC PATHOLOGY IN RA

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Background: Rheumatoid arthritis (RA) is a chronic inflammatory disease associated with substantial local and systemic bone loss. Despite the availability of several treatment options many patients do not reach low disease activity. Furthermore, current therapeutics generally target inflammation rather than erosive pathology. Thus, there remains a need for new therapies that can target both aspects of the disease. Prior studies have shown that biphenylcarboxylic acid small molecule derivatives not only inhibit murine osteoclastogenesis but also attenuate inflammation and bone destruction in murine models of RA^{1,2}.

Objectives: To evaluate a novel small molecule derivative, MBS2133, on human osteoblastogenesis, osteoclastogenesis and cellular function, and to investigate the *in vitro* mechanism-of-action.

Methods: Osteoblasts were derived from human mesenchymal stem cells. Cells were differentiated in the presence or absence of MBS2133 and mineralization assessed by Alizarin Red staining. Human CD14⁺ blood monocytes were differentiated into osteoclasts (OCs) with M-CSF and RANK-L, in the presence or absence of MBS2133, and/or metabolites. Mature OCs were stained with tartrate-resistant acid phosphatase (TRAP) and quantified by light microscopy. Osteolytic activity was assessed on mineral-coated surfaces. Western blot analysis was used to assess downstream signalling pathways. Changes in the metabolic profile of pre-osteoclasts following 4h exposure to MBS2133 was carried out by liquid chromatography mass spectrometry.

Results: MBS2133 had no effect on the differentiation and function of primary human osteoblasts. In comparison, exposure of RANK-L stimulated CD14⁺ monocytes to MBS2133 significantly reduced OC differentiation and osteolytic activity of mature OCs. Notably, exposure of pre-OCs to MBS2133 for 2h at initiation of osteoclastogenesis, was sufficient to significantly reduce subsequent OC differentiation. Evaluation of treated pre-osteoclasts revealed that RANKL-mediated phosphorylation of p38 was reduced. Metabolomic analysis of pre-osteoclasts revealed that MBS2133 induced a substantial reduction in a range of metabolites associated with glycolysis, oxidative phosphorylation and fatty acid oxidation pathway. Notably, L-carnitine, which facilitates the transportation of fatty acids to the mitochondrial matrix and enables processing and entry into tricarboxylic acid (TCA) cycle for further energy production, was significantly reduced. *In vitro* supplementation of L-carnitine inhibited the ability of the compound to switch off OC differentiation and osteolytic activity.

Conclusion: The results of this study demonstrate that MBS2133 specifically modulates the metabolome of myeloid cells, which has a substantial impact on their ability to differentiate into mature osteoclasts. These findings highlight the importance of modulating the glycolysis/oxidative phosphorylation axis in osteoclastogenesis and suggest that targeting the metabolic state of pre-osteoclasts could offer a new therapeutic approach to treat bone resorption in rheumatic diseases.

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SAT0046

ARE SENSE OF SOCIAL SUPPORT AND LOW DECISION LATITUDE AT WORK LINKED TO RISK OF RHEUMATOID ARTHRITIS, AND IF SO, HOW DO THEY RELATE TO OTHER RISK FACTORS? RESULTS FROM THE SWEDISH EIRA STUDY

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Background: The role of psycho-social factors in the development of rheumatoid arthritis (RA) is debated.

Objectives: We investigated whether psychosocial stress measured as low sense of social support, and low decision latitude at work, were linked to risk of RA, and whether they related to known lifestyle risk factors for RA.

Methods: The Swedish population-based EIRA study included incident RA cases (N=3724) and controls (N=5937), matched for age, sex and residential area. Responders filled in questionnaires regarding self-reported social support, decision latitude at work and life-style-factors.

The distribution of answers among controls were used to define exposure, thus for social support, those in the lowest quartile of social support were considered exposed to low social support and similarly for decision latitude, those in the lowest quartile were considered exposed to low decision latitude at work.

Using logistic regression, we first evaluated whether exposures associated with RA risk, considering potential confounding of established risk factors. Then, we investigated whether the frequency of those factors differed between individuals reporting low social support or low decision latitude at work or not, among cases and controls.

Results: There were 898 cases with low social support and 285 cases with low decision latitude at work (latter only available in first part of EIRA).

Low social support was not associated with RA risk in unadjusted analyses (OR= 1.05, 95%CI=0.95-1.15). Low decision latitude at work did associate with a higher RA risk in the unadjusted analyses (OR=1.52, 95% CI=1.20-1.94), but this association was no longer significant after further adjustment for smoking, obesity and university degree (adjusted OR=1.24, 95% CI=0.93-1.63). Associations between those life-style risk factors and RA were confirmed (no university degree, OR=1.50; smoking OR=1.71; obesity OR=1.15).

Next, we evaluated whether low social support or low decision latitude at work differed by previously established risk factors. Cases with RA reporting low sense of social support were more often men (OR=1.60, 95% CI=1.40-1.83), current smokers (OR=1.46, 95%CI=1.26-1.70), obese (OR=1.29, 95%CI=1.09-1.54), physically inactive (OR=2.78, 95%CI=1.98-3.90) and without a university-degree (OR=2.04, 95%CI=1.77-2.36); with similar pattern among the controls. For working-conditions, cases reporting low decision latitude at work were also more often current smokers (OR=2.05, 95%CI=1.33-3.16) and with no university degree (OR=8.23, 95%CI=5.13-13.22), but less often male (OR = 0.40, 95%CI=0.26-0.60). Again, the pattern was similar among controls. RF/ACPA-positivity did not associate with low social support or low decision latitude.

Conclusion: Neither low social support nor low decision latitude at work were associated with an increased risk of RA after adjustment for other known lifestyle risk factors for RA. An initial crude association between