reported to ameliorate arthritis in several mice models. Mechanistic target of rapamycin (mTOR) pathway and glutaminolysis activate cooperatively in the differentiation from myeloid progenitors to mature myeloid cells such as dendritic cells, macrophages, or osteoclasts as well as the activation of effector T cells and the differentiation of Th1 and Th17 cells. Although rapamycin has reported to facilitate the expansion of MDSCs and their immunosuppressive ability, the effect of the inhibitor of glutaminolysis on MDSCs is still unknown.

Objectives: The aim of this study is to evaluate the facilitative effects of the inhibition of mTOR pathway and glutaminolysis on MDSCs in a mouse model of rheumatoid arthritis.

Methods: Bone marrow (BM) cells from untreated Balb/c mice were cultured for 5 days under granulocyte-macrophage colony-stimulating factor (GM-CSF) stimulation with four patterns of drugs; 1) DMSO (control), 2) rapamycin (Rapa), 3) 6-Diazo-5-oxo-L-norleucine (DON; a glutamine antagonist), or 4) the combination of rapamycin and DON (Rapa +DON). Cultured BM cells were analysed by flow cytometry. Cultured MDSCs were isolated by manual MACS and analysed their immunosuppressive characters by co-culture with CFSE-dyed CD4⁺ T cells. Rapa or Rapa +DON were administered intraperitoneally to arthritic SKG mice induced by Zymosan A injection.

Results: We found that DON suppressed the differentiation of dendritic cells (DC) in a dose-dependent manner and the addition of Rapa on DON inhibited the differentiation of macrophages *in vitro*. The proportions of the phenotype of MDSCs were increased with administrations of Rapa or DON, and large part of them were Ly6G⁺ cells (the phenotype of polymorphonuclear MDSCs; PMN-MDSCs). Rapa ±DON significantly increased the expressions of TGF-β and PD-L1 and the inhibitory capacity of Ly6G⁺ PMN-MDSCs. Rapa +DON significantly suppressed arthritis more efficiently in SKG mice than Rapa *in vivo*. (see figure 1)

Conclusions: The combination of rapamycin and a glutamine antagonist facilitates the expansion of PMN-MDSCs *in vitro* and ameliorates arthritis in SKG mice *in vivo*.

Disclosure of Interest: None declared

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THU0099 MYELOID SIRTUIN 6 DEFICIENCY ACCELERATES EXPERIMENTAL AND HUMAN ARTHRITIS BY INCREASING MACROPHAGE INFILTRATION INTO SYNOVIUM

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Background: Rheumatoid arthritis (RA) is an autoimmune inflammatory disease of the joints and is characterised by immune cell infiltration, synovial hyperplasia, and destruction of cartilage and underlying bone¹. Myeloid derived monocytes and macrophages secrete a variety of cytokines such as tumour necrosis factor-α (TNF-α), interleukin (IL)-1β and IL-6, all of which perpetuate and amplify the vicious cycle of chronic inflammatory pathways². Indeed, macrophage numbers in the synovium and serum levels of monocyte-derived cytokines correlate well with clinical symptoms and degree of joint damage in RA³.

Objectives: We recently reported that myeloid sirtuin 6 (Sirt6) is a critical determinant of phenotypic switching and the migratory responses of macrophages⁴.

Given the prominent role of macrophages in rheumatoid arthritis (RA) pathogenesis⁵, we tested whether myeloid Sirt6 deficiency affects the development and exacerbation of RA.

Methods: Arthritis was induced in wild type and myeloid Sirt6 KO (mS6KO) mice using collagen-induced and K/BxN serum transfer models. Peripheral blood mononuclear cells (PBMC) and synovial fluid macrophages were obtained from patients with RA and osteoarthritis and used for comparisons of Sirt6 expression and inflammatory activities.

Results: Based on clinical scores, ankle thickness, pathology and radiology, arthritis was more severe in mS6KO mice relative to wild type with a greater accumulation of macrophages in the synovium. Consistently, myeloid Sirt6 deficiency increased the migration potential of macrophages toward synovial cells-derived chemoattractants. Mechanistically, Sirt6 deacetylates forkhead box protein O1 to trigger its nuclear export and proteasomal degradation. Lastly, PBMC and macrophages isolated from RA patients exhibited lower Sirt6 expression compared with those from osteoarthritis patients or healthy subjects and their Sirt6 activity was inversely correlated with disease severity of the patients.

Conclusions: Our data identify a role of myeloid Sirt6 in clinical and experimental RA and suggest that myeloid Sirt6 may be an intriguing therapeutic target.

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Rheumatoid arthritis – prognosis, predictors and outcome

THU0100 WORK IMPAIRMENT IN RHEUMATOID ARTHRITIS IS HIGHLY CORRELATED WITH DEPRESSION

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Background: Work outcomes are highly relevant in rheumatoid arthritis. Almost a third of people are no longer in employment by 2 years after diagnosis. Remaining in the workforce has positive attributes in terms of health outcome and quality of life.

Objectives: We set out to study the relationship between work and depression in rheumatoid arthritis.

Methods: We used routinely collected data from a hospital rheumatoid arthritis cohort that has systematically collected longitudinal data on disease measures, mental health, and work impairment. The Work and Social Adjustment Scale was used to estimate work impact, and we used question 2 (scale 0–8, above 6 indicating severe impairment) for analyses. Mood was assessed using the PHQ2. Cross sectional analyses were used to describe the relationship between work impairment and depression, adjusting for disease severity factors. We then analysed the temporal relationship between work impairment and mood.

Results: In total 283 patients had data available for analysis. Mean age was 53 years (SD 15), 81% were female, median disease duration 6 years (IQR 0 to 10). 74% were seropositive (RF or CCP), mean baseline DAS28 score 3.8 (SD 1.7), baseline HAQ 1.2 (SD 0.9). At baseline 69% reported no depression, 13% reported some symptoms, 18% had probable major depression. 72% of patients reported some degree of work impairment, 14% reported severe impairment. There was a strong relationship between baseline depressive symptoms and work impairment: coefficient 2.4, 95% CI 1.7 to 3.0, p<0.001. Adjusting for age, gender, DAS28, HAQ: 1.3, 95% CI 0.5 to 2.0, p=0.004. Over time work impairment increased (linear regression coefficient: 0.2 per year 95% CI 0.1 to 0.4), see figure 1. People with baseline low mood had an accelerated worsening of work impairment.