**Objectives** This study aimed to assess whether peripheral monocytes in RA are pre-programmed to become M1 pro-inflammatory macrophages.

**Methods** Blood was collected from healthy donors, at-risk individuals (Those with arthralgia, ACPA+/RF+, normal CRP and no evidence of synovitis) and established RA patients. CD14+ monocytes were isolated from peripheral blood mononuclear cells using a CD14 magnetic bead separation kit. Cells were stimulated with LPS (100 ng/ml) for 3–24 hours and to assess the effects of STAT3 inhibition, cells were pre-treated with STAT3IC (10 μM) for 30 mins. A Human Cytokine and Chemokine PCR array was carried out and those genes most differentially expression were further validated in a larger cohort of patients using RT-qPCR. The metabolic profile of cells was analysed using Seahorse XFE Technology, which concomitantly analysis glycolysis and mitochondrial respiration in real-time. Gene and protein expression of key inflammatory and glycolytic markers was also carried out by RT-qPCR, western blotting and ELISA.

**Results** CD14+ RA monocytes are hyper-inflammatory upon stimulation, with significantly higher expression of IL-1β, TNFα, IL-6, IL-27, CXCL10 and CXCL11 compared to healthy controls, which is indicative of a M1-like pro-inflammatory phenotype. These hyper-inflammatory monocytes are highly glycolytic, with increased expression of HIF1α, HK and PFKFB3, key glycolytic enzymes. Both baseline glycolysis and baseline oxidative phosphorylation are increased in RA CD14+ monocytes, paralleled by increased ATP synthesis and maximal respiratory capacity, suggesting a hyper-energetic phenotype. This hyper-inflammatory, hyper-glycolytic phenotype is mediated by STAT3, as selective STAT3 inhibition can significantly decrease M1-like cytokines and PFKFB3 and HK2 expression. In addition, STAT3 inhibition significantly decreases both oxidative phosphorylation and glycolysis pathways. Finally, this pro-inflammatory phenotype in evident in CD14+ monocytes from arthralgia ACPA+/RF+ people at risk of developing disease, demonstrating that these processes may precede clinical manifestations in RA.

**Conclusions** This study demonstrates the unique inflammatory and metabolic phenotype of RA monocytes, suggesting that peripheral CD14+ monocytes may be pre-programmed to become M1-like pro-inflammatory macrophages. In addition, the observation of this phenotype in at-risk individuals indicates that these features may precede clinical manifestations of RA and therefore could be useful as a biomarker for early diagnosis.

**Disclosure of Interest** None declared.