Investigating the Oncostatin-M signalling pathway as a stratification tool in early inflammatory arthritis

Authors: Ben Millar, Nicola Maney, Najib Naamane, Oliver Eltherington, Amy E Anderson, Katherine Nevin, Eszter Csomor, Shaun Flint, Drew Rowan, John D Isaacs & Arthur Pratt

Background. Seronegative inflammatory arthritis (SIA) describes an often-overlooked spectrum of immune-mediated peripheral joint disease in which circulating autoantibodies are absent; it includes psoriatic arthritis, autoantibody negative rheumatoid arthritis (RA), and undifferentiated inflammatory arthritis (UIA) patients. Oncostatin-M (OSM) up-regulation is a recognised feature of human inflammatory arthritis, and its over-expression in mice leads to synovial hyperplasia. Its role is established in the pathogenesis of inflammatory bowel disease (IBD) and skin psoriasis which frequently co-present with SIA. We hypothesise that OSM signalling pathway activation defines an "endotype" of SIA patients that spans traditional disease classifications and may be therapeutically targeted.

Methods. Patients were enrolled for a pilot study from the Northeast Early Arthritis Cohort (NEAC). Serum samples from 38 SIA patients, 25 autoantibody seropositive RA patients (SPRA) matched for markers of systemic inflammation, and 34 osteoarthritis (OA) controls were analysed for OSM, TNFα and IL-6 using the Meso Scale Discovery platform; all patients were treatment naive at the time of blood draw. Contemporaneous T-cell / B-cell transcriptomic data is archived for each sample. Formalin-fixed paraffin-embedded synovial tissue was obtained from a NEAC subset of 49 individuals using a minimally-invasive technique, and subjected to H&E/IHC staining.

Results. Serum measurements showed elevated OSM in inflammatory arthritis vs non-inflammatory OA ($p=0.033$) with no apparent difference according to autoantibody status. Linear regression of SIA OSM levels against Baseline DAS-ESR demonstrated a positive correlation ($r=0.332$; $p=0.04$). IL-6 levels (but not TNF levels) were higher in SIA patients ($p<0.01$). Morphological examination of NEAC cohort synovial tissue demonstrates a reduction in overall synovitis in SIA vs SPRA ($p<0.05$) according to an established scoring system. Ongoing work using multiplex immunofluorescence will establish expression patterns of OSMR in the cohort but initial work suggests expression in macrophages and the stromal compartment predominates.

Conclusion. Our preliminary data indicate that the synovial architecture of inflammatory arthritis differs according to autoantibody status. Prominent expression of OSMR in stromal cell populations suggests OSM signaling in synovial fibroblasts, a key population in RA. These data will inform downstream analyses. The lack of clear difference between groups in the peripheral blood data suggests that OSM is acting locally rather than peripherally.