

Methods: Micromass cultures of C28/12 chondrocytes and C3H10T1/2 mesenchymal cells were employed to determine the ability of PGRN fragments to stimulate chondrogenesis. HT-29 and WEHI-164 TNF sensitive cells were used to evaluate the anti-TNF capacity of LAP-PGRN fragments. Co-immunoprecipitation was used to characterise interactions between PGRN fragments and TNFR1. DBA/1 fibroblasts transduced with lentivirus encoding LAP-PGRN fusions were delivered to DBA/1 mice with CIA to assess anti-arthritis effects.

Results: PGRN, LAP-PGRN, LAP-GRN A and LAP-Atsttrin were cloned and expressed in mammalian expression systems. PGRN elevated sulphated proteoglycan production in micromass cultures of C28/12 human chondrocytes, and also stimulated proliferation of C3H10T1/2 cells. Furthermore, PGRN reduced TNF-mediated catabolism of extracellular matrix in established chondrogenic C3H10T1/2 micromass cultures. LAP-PGRN, LAP-GRN A and LAP-Atsttrin potentiated BMP2 mediated chondrogenesis in C3H10T1/2 micromasses. PGRN failed to protect WEHI-164 fibroblasts or HT-29 colorectal carcinoma cells from TNF-mediated cytotoxicity despite interacting with TNF receptor *in vitro* by co-immunoprecipitation. LAP-PGRN, LAP-GRN A and LAP-Atsttrin all failed to protect WEHI-164 cells from TNF-mediated cytotoxicity, even after MMP1 cleavage and release. CIA disease progression was reduced in DBA/1 mice treated with autologous fibroblasts overexpressing murine Etanercept or PGRN relative to control treatment. LAP-Atsttrin was more effective than LAP-PGRN and LAP-GRN A at reducing arthritic symptoms relative to LAP-Empty controls.

Conclusions: These findings suggest that PGRN could be used as a targeted dual-function chondrogenic and anti-inflammatory treatment for RA, but these effects are not elicited directly through the TNF pathway.

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THU0042 LONGITUDINAL IP-10 SERUM LEVELS ASSOCIATE WITH THE COURSE OF DISEASE ACTIVITY AND ACHIEVING DMARD-FREE SUSTAINED REMISSION IN RHEUMATOID ARTHRITIS

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Background: Although rheumatoid arthritis (RA) is a chronic autoimmune disease that is persistent in the majority of patients, 10–15% of the RA patients achieve disease modifying anti-rheumatic drugs (DMARD)-free sustained remission over time. Biological mechanisms underlying the persistence of inflammation in RA are yet unidentified. It is well established that increased serum levels of IFN- γ -induced protein 10 (IP-10) are associated with (acute) increased inflammatory responses against mycobacterial pathogens causing leprosy and tuberculosis, thereby providing useful diagnostic tools in these infectious diseases. Based on previous genetic susceptibility studies, we hypothesize that there is an overlap between inflammatory responses observed in these mycobacterial diseases and those observed in RA. Therefore, we determined the association between serial IP-10 serum levels and achieving DMARD-free sustained remission as well as disease activity scores (DAS)-remission.

Objectives: To 1) assess the association between IP-10 levels over time in patients that have persistent RA versus patients that achieve DMARD-free sustained remission, and 2) determine the association between IP-10 levels and DAS.

Methods: 139 serum samples of 34 RA-patients (1987-criteria), obtained at the time of diagnoses and at yearly intervals thereafter, were studied. 15 patients had persistent RA and 19 patients achieved DMARD-free sustained remission after a median follow up of 2.7 years. IP-10 serum levels were measured using a previously developed, user-friendly lateral flow assay. Baseline and change in IP-10 levels over time were compared between patients with persistent RA and those achieving DMARD-free sustained remission. The association between the change in IP-10 level and the change in DAS was studied; in addition the course of the absolute IP-10 levels and the DAS over time was plotted for individual patients.

Results: IP-10 serum levels varied from 316 – 53,685 pg/ml between RA-patients. Patients that had persistent arthritis or achieved DMARD-free sustained remission over time did not differ in baseline IP-10 levels (median persistent RA 1991 pg/ml and median DMARD-free sustained remission 3292 pg/ml, $p=0.19$). However, a significant decrease in IP-10 levels over time was observed in patients achieving DMARD-free sustained remission ($p=0.003$), whereas IP-10 levels remained stable in patients with persistent RA. Changes in IP-10 levels correlated well with changes in DAS scores ($p=0.05$). Also at the level of individual patients, a strong correlation between IP-10 levels and DAS over time was observed.

Conclusions: These longitudinal data indicate that IP-10 levels are associated with perseverance of RA as well as with disease activity. Rapid diagnostic tests measuring IP-10 levels can therefore be helpful in monitoring of RA patients.

Disclosure of Interest: None declared

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THU0043 TARGETED MEDICINE: THERAPEUTIC USE OF FUNCTIONAL CYTOKINE ASSAYS IN COMPLEX INFLAMMATORY ARTHRITIS

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Background: Functional cytokine assays have been limited to experimental models of inflammatory arthritis without translation into clinical therapy.

Objectives: To illustrate the successful use of functional cytokine assays in providing targeted treatment for complex inflammatory arthritis.

Methods: A 24 year old male presented in 2014 with a florid asymmetrical polyarthritis associated with an elevated acute phase response (ESR 50, CRP 42, ALP 132). He had no history of psoriasis, inflammatory bowel or eye disease and no family history.

Vasculitis and viral arthritis screen, ACE, ANA, Anti dsDNA, RF and CCP were negative. He was positive for HLA B27 without evidence of spondyloarthropathy on imaging. He was noted to have a monoclonal gammopathy of uncertain significance with normal bone profile, unremarkable urinary BJP and whole body CT scan. His joint symptoms responded to corticosteroid therapy with the addition of hydroxychloroquine and methotrexate. In 2015, his clinical condition had significantly deteriorated with worsening joint inflammation, 3 kg weight loss with a sudden rise in acute phase response, without proven infection. His functionality declined with long term sickness from work.

Biochemical tests revealed: Hb 123, MCV 87.2, Plt 393, Neutrophil 7.76, ESR 86, Alb 31, Calcium 2.68, ALP 387 (noted to be of bony origin), CRP 286, Ferritin 1161, PT 13, and APTT 39. Renal function, protein electrophoresis, blood film, haemolytic screen, viral and autoimmune liver screens were unremarkable. Hydroxychloroquine and methotrexate were temporarily with-held at this stage, although he was maintained on prednisolone 20 mg, with a partial response in his joint symptoms. An infiltrative pathology was a concern and was subsequently excluded.

The next therapeutic step would have been an anti-TNF agent. Nevertheless, due to his atypical and complex disease course, cytokine assays were performed to further characterise his disease profile and provide targeted treatment. Results showed an elevated IL6 production; IV Tocilizumab was selected for the treatment of his inflammatory arthritis. He has had a remarkable response in terms of his systemic and joint symptoms as well as considerable biochemical improvement. He was able to de-escalate his corticosteroid regime and return to work.

Results: TNF alpha, IL1 beta, and IL-6 are important inflammatory mediators and targets of intervention in the treatment of Rheumatoid arthritis. They may be induced *in vivo* and *in vitro* using Toll like receptor mediated innate activation. Active Whole Blood Cytokine Profiling was performed for the patient and compared to healthy controls. Innate activation of whole blood with various TLR agonists including LPS (TLR4), PAM3 (TLR1/2), Imiquimod (TLR7) revealed low induction of TNF alpha and IL1 beta in the patient when compared to controls. In contrast, the patient showed an elevated IL-6 production. Patient's cytokine levels in serum and in non-activated whole blood were normal.

Conclusions: Our case highlights the potential progression to personalised medicine in achieving optimal patient outcome delivered in a cost-effective way.

Functional cytokine assays in the appropriate context and within selected patient groups can help to achieve disease remission by allowing targeted treatment.

Disclosure of Interest: None declared

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THU0044 CHONDROITIN SULPHATE INHIBITS MONOCYTE CHEMOATTRACTANT PROTEIN-1 RELEASE FROM 3T3L1 ADIPOCYTES: A NEW TREATMENT OPPORTUNITY FOR OBESITY-RELATED METABOLIC SYNDROMES?

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Background: Monocyte chemoattractant protein-1 (MCP-1) overproduction from inflamed adipose tissue is a major contributor to obesity-related metabolic syndromes. We have recently published that chondroitin sulphate (CS) can attenuate the monosodium urate (MSU) crystal mediated THP-1 macrophage inflammatory response reflected by reduced release of pro-inflammatory cytokines IL-1 β and TNF α . We have also recently determined that the CS inhibitory effect is not acting at the inflammasome but upstream, most likely by inhibiting activation of NF- κ B.

Objectives: We sought to determine whether CS had a similar inhibitory effect on MCP-1 release from lipopolysaccharide (LPS) stimulated adipocytes.

Methods: We cultured 3T3-L1 embryonic fibroblasts and induced their differentiation into adipocytes using an established protocol. We then treated the adipocytes with LPS to induce inflammation and thus MCP-1 release. At the same time we added varying concentrations of CS (Bioiberica, Spain) in a physiologically relevant range (10–200 μ g/ml) and 24h after we measured MCP-1 release (R&D Systems, Minneapolis, MN, USA). We also cultured THP-1 monocytes and tested whether CS (200 μ g/ml) could inhibit cell migration induced by human recombinant MCP-1. Monocyte chemotaxis in response to 24h exposure to