miRs showed no significant difference in fold change between jSpA patients and healthy controls.

Table 1. Results of DNA promoter methylation and previously performed gene expression analysis in juvenile spondyloarthritis patients¹

GENES	Fold Enrichment of Immunoprecipitated DNA		Fold Change of Expression ¹	
	Controls (n=7)	p	Fold Change	p
Patients (n=19)				
TLR4	0213	0153	0,5759	+3,91 <0,01
NLRP3	11,24	5412	0,0220	-5,00 <0,01
CXCR4	0303	0170	0,2658	+1,87 <0,01
PTPN12	0338	0202	0,3768	-2,63 <0,01

Conclusions: Our study indicated epigenetic modifications are probably responsible for some of the expression alterations in jSpA patients in the initial phase of the disease. Since NLRP3 has a crucial role in inflammasome assembly and inflammasomes have been shown to shape microbiota, it is reasonable to assume dysbiosis in jSpA patients can at least partially be explained by reduced NLRP3 expression due to hypermethylation, stressing for the first time the epigenetic contribution to jSpA pathophysiology. While it is still not clear if these epigenetic alterations are caused by genetic mutations in epigenetic factors or exposure to certain environmental factors that mediate the occurrence of aberrant epigenetic profiles, the discovery of DNA methylation-based signature of the NLRP3 gene could have important implications in addressing extrinsic and intrinsic contribution to jSpA pathophysiology, whereas the possibility of reverting epigenetic modifications opens whole new prospects for therapeutic treatment of this complex disease.

REFERENCE:

- [1] Lamot L, Borovecki F, Tambic Bukovac L, Vidovic M, Perica M, Gotovac K, et al. Aberrant expression of shared master-key genes contributes to the immunopathogenesis in patients with juvenile spondyloarthritis. *PLoS ONE* 2014;9(12):e115416.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.2326

FRI0004

GRANULOCYTE MACROPHAGE COLONY STIMULATING FACTOR IS SECRETED AT HIGHER LEVELS FROM STIMULATED MONOCYTE-DERIVED MACROPHAGES FROM PATIENTS WITH ENTHESTITIS RELATED ARTHRITIS AND IS SIGNIFICANTLY ENHANCED BY THE UNFOLDED PROTEIN RESPONSE

C. Fisher^{1,2}, D. Eleftheriou¹, D. Sen^{1,2}, Y. Ioannou¹. ¹Arthritis Research UK Centre for Adolescent Rheumatology, University College London; ²National Institute for Health Research University College London Hospitals Biomedical Research Centre, University College London and University College London Hospital, London, UK

Background: Entesitis related arthritis (ERA) is a subtype of juvenile idiopathic arthritis exhibiting many similarities to the adult spondyloarthropathies (SpA). The innate immune system and intracellular stress responses, including the unfolded protein response (UPR), have been implicated in the pathogenesis of SpA. Granulocyte macrophage colony stimulating factor (GM-CSF), as well as being a haemopoietic growth factor, plays a central role in regulating innate immunity and has recently been implicated in the pathogenesis of SpA¹ but has not been studied in ERA.

Objectives: To compare levels of GM-CSF produced by monocyte-derived macrophages (MDMs) from patients with ERA and healthy controls and to observe the effect of inducing the UPR on those levels.

Methods: Peripheral blood monocytes were isolated from 39 patients with ERA (68% HLA B27 positive, 84% male, median age 16 years 4 months, median disease duration 3 years 10 months) and 21 age and gender-matched healthy controls and differentiated *in vitro* with macrophage-colony stimulating factor. Cells were treated with interferon gamma for 24 hours to upregulate HLA B, washed and then stimulated with lipopolysaccharide (LPS) alone (50 ng/mL) or LPS and tunicamycin (TM) (5 µg/mL), an inducer of the unfolded protein response. GM-CSF was measured from the cell culture supernatants after 24 hours culture by luminex assay.

Results: Levels of GM-CSF at baseline were similar in patients and healthy controls [median 121.3 pg/mL (IQR 96.6–194.0 pg/mL) vs 157.1 pg/mL (124.2–203.3 pg/mL), p=0.1]. However, with LPS stimulation, MDMs from patients secreted significantly higher levels of GM-CSF [median 1853 pg/mL (IQR 1206–3061 pg/mL) vs 1342 pg/mL (IQR 713.3–1797 pg/mL), p=0.0057]. On stimulation with TM in addition to LPS, GM-CSF production was further enhanced in both patients and healthy controls [median 9027 pg/mL (IQR 4746–13961 pg/mL) vs

3834 pg/mL (IQR 1603–9158 pg/mL)] and remained significantly higher in patients (p=0.0096). To investigate the effect of the UPR, fold change in GM-CSF was calculated for each sample between MDMs stimulated with LPS alone and MDMs stimulated with both LPS and TM. Median fold change in patients was 3.95 (IQR 1.54–5.47) and 2.36 (IQR 0.49–4.69) in healthy controls. Interestingly, MDMs from patients who were HLA B27 positive exhibited significantly higher median fold change in GM-CSF with UPR induction compared to HLA B27 negative patients [4.14 (IQR 2.22–6.10) vs 1.33 (IQR 0.36–3.91), p=0.0098]. No associations were seen with different treatment regimes in the patient group.

Conclusions: MDMs from patients with ERA produce significantly higher levels of GM-CSF after stimulation compared to healthy controls and this is further enhanced by the UPR, especially in HLA B27 positive patients. These results potentially implicate GM-CSF in the pathogenesis of ERA and thus further support the concept of GM-CSF as a novel target for treatment in certain subgroups of patients.

REFERENCE:

- [1] Al-Mossawi MH, Chen L, Fang H, Ridley A, de Wit J, Yager N, et al. Unique transcriptome signatures and GM-CSF expression in lymphocytes from patients with spondyloarthritis. *Nat Commun* 2017 Nov 15;8(1):1510.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.5457

FRI0005

THE RELATIONSHIP BETWEEN JUVENILE SYSTEMIC LUPUS ERYTHEMATOSUS AND THE TRANSCRIPTION FACTORS NF-KAPPAB AND PPAR-GAMMA

S. Sahin¹, S. Dumus², A. Adrovic¹, K. Barut¹, R. Gelisgen², H. Uzun², O. Kasapcopur¹. ¹Pediatric Rheumatology; ²Department of Biochemistry, Istanbul University, Cerrahpasa Medical School, Istanbul, Turkey

Background: Systemic lupus erythematosus (SLE) is an autoimmune disease characterised by high-levels of autoantibodies mainly targeting nuclear antigens and loss of self-tolerance. Peroxisome-proliferator activated receptor gamma (PPARγ) and nuclear factor-kappa beta (NF-κB) are transcription factors, which, within normal levels, have shown to be crucial in immunomodulation namely, activation and development of normal lymphocytes, negative and positive selection of T and B cells. High-levels of NF-κB has inflammatory properties such as release of autoreactive T cells. On the contrary, PPARγ has anti-inflammatory effects, which has been demonstrated to be effective when used early in prevention of disease in murine models of systemic lupus erythematosus.

Objectives: Herein, we investigated whether NF-κB and PPARγ could exert opposite effects in the immune response and the possible implications in immunomodulation of juvenile systemic lupus erythematosus.

Methods: Serum NF-κB and PPARγ levels were measured in 42 juvenile systemic lupus erythematosus. In addition, 19 juvenile systemic sclerosis and 25 age-matched healthy children were selected for patient control and healthy control, respectively. We have also assessed the relation of these transcription factors with disease activity and anti-ds DNA.

Results: The control group did not differ from the juvenile SLE and juvenile systemic sclerosis patients for age (p>0.05). According to our study, serum NF-κB levels of juvenile SLE and juvenile systemic sclerosis patients were significantly higher (1.87±1.0 and 2.17±1.0 versus 1.25±0.7), while serum PPARγ levels were significantly lower than that of healthy controls (1.58±0.6 and 1.52±0.5 versus 2.03±0.9). The difference was not significant between juvenile systemic lupus erythematosus and juvenile systemic sclerosis. In patients with juvenile systemic sclerosis serum NF-κB levels negatively correlated with serum PPARγ levels (R=-0.49; p=0.032); however, this relationship was not observed in juvenile SLE patients and healthy controls.

Conclusions: Increased serum NF-κB levels represent upregulated signalling cascades, so it is associated with increased levels of pro-inflammatory cytokines. Since juvenile systemic sclerosis and juvenile systemic lupus erythematosus are autoimmune diseases, patients had high levels of NF-κB and low levels of PPAR than controls, as expected. Previous studies revealed that PPARγ activation inhibits NF-κB transcriptional activity. Correlation results in juvenile systemic sclerosis cohort are compatible with this finding, however not in juvenile systemic lupus erythematosus patients. This could be due to the limited number of patients. Further studies with large number of patients are needed to better elucidate the implication of these transcription factors in therapeutic pathways.

REFERENCES:

- [1] Zubair A, Frieri M. NF-κB and systemic lupus erythematosus: examining the link. *J Nephrol* 2013;26(6):953–9.
[2] Hayden MS, Ghosh S. NF-κB, the first quarter-century: Remarkable progress and outstanding questions. *Genes Dev* 2012;26(3):203–234.