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.

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FRI0004

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

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Background: Entersitis 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.

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FRI0005

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

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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.

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FRI0006

ASSOCIATION BETWEEN INTERLEUKIN-10 POLYMORPHISMS AND JUVENILE IDIOPATHIC ARTHRITIS: A META-ANALYSIS

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Background: Juvenile idiopathic arthritis (JIA) is the most common chronic arthritis in children. JIA is a heterogeneous group of complex diseases and the result of a combination of genetic and environmental factors. Multiple genes contribute to the risk of developing JIA. Interleukin-10 (IL-10) is an anti-inflammatory cytokine that is associated with inflammatory diseases. IL-10 is considered a candidate gene for JIA based on its chromosomal location and functional relevance.

Objectives: IL-10 genetic polymorphisms associated with JIA were previously identified, especially in haplotypes studies. However, results from different studies have been inconsistent. Thus, we investigated whether IL-10 polymorphisms were associated with susceptibility to JIA.

Methods: A meta-analysis was conducted of the associations between the IL-10–1082G/A, –819 C/T, and –592 C/A polymorphisms and JIA. A total of eight studies involving 1495 patients and 1670 controls were considered in the meta-analysis. This meta-analysis was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Results: There was no association between the IL-10–1082G/A, –819 C/T, and –592 C/A polymorphisms and JIA in allele contrast and any of the genetic models (allele contrast: OR=0.90, 95% CI=0.79–1.02, p=0.09; OR=0.97, 95% CI=0.83–1.13, p=0.68; OR=0.92, 95% CI=0.81–1.06, p=0.24, respectively). Subgroup analyses revealed a significant association between the IL-10–1082 G allele and systemic JIA (OR=0.80, 95% CI=0.67–0.96, p=0.02). Meta-analysis of the IL-10 haplotype revealed no association between GCC, ACC, and ATA haplotypes and JIA.

Abstract FRI0006 – Figure 1. ORs and 95% CIs of the individual studies and pooled data for the associations between the IL-10 -1082 G allele and systemic JIA

Conclusions: This meta-analysis indicated lack of associations between IL-10 polymorphisms and susceptibility to JIA. However, there was a significant association between IL-10–1082 G allele and systemic JIA.

Abstract FRI0007 – Table 1

	N	Summary Random Effect Model		DOR Random Effect Model			Adjusted RDOR Random Effect Model		
		Sensitivity	Specificity	DOR	IC 95%	p	RDOR	IC 95%	p
Total	16	0.75	0.72	11.5	(6.5–20.1)	<0.001	1.15	(0.9–1.4)	0.117
Year before 2013	5	0.64	0.89	20.6	(4.5–94.4)	0.001	15.7	(4.8–51.8)	0.001
2013 and after	11	0.80	0.65	9.2	(5.2–16.2)	<0.001	1.0		
Countries in Asia	4	0.88	0.74	23.6	(8.8–63.5)	0.098	10.4	(3.2–33.7)	0.002
Countries in Europe	12	0.70	0.71	8.9	(4.7–17.5)	<0.001	1.0		
Joint included									
MCP	12	0.79	0.74	16.0	(8.1–31.9)	<0.001	11.3	(3.0–41.9)	0.003
MTP	4	0.78	0.67	9.6	(5.1–18.2)	<0.001	2.8	(1.2–6.3)	0.021
Wrist	11	0.82	0.73	18.6	(8.4–40.9)	<0.001	1.0		
Cutoff criteria									
GS≥1	6	0.86	0.57	16.5	(9.6–28.3)	0.503	6.0	(1.6–22.5)	0.009
GS≥2	5	0.66	0.69	5.6	(2.9–10.5)	0.025	2.4	(0.7–7.6)	0.139
GS≥3	3	0.74	0.79	12.9	(5.6–29.9)	0.314	3.1	(0.7–14.1)	0.132
PD≥1	9	0.67	0.72	7.9	(4.3–14.9)	0.003	3.9	(1.3–11.7)	0.018
PD≥2	7	0.73	0.77	9.6	(4.1–22.5)	<0.001	3.3	(0.9–11.8)	0.059
PD≥3	6	0.38	0.84	4.5	(5.2–9.4)	<0.001	2.0	(0.29–14.4)	0.462
Tenosynovitis	3	0.27	0.65	0.73	(0.01–82.8)	<0.001	1.0		
Erosions	6	0.40	0.84	3.3	(1.7–6.2)	0.242	1.0		

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Rheumatoid arthritis – prognosis, predictors and outcome

FRI0007

PERFORMANCE OF MUSCULOSKELETAL ULTRASONOGRAPHY (MSUS) AND OPTIMAL CUTOFF CRITERIA FOR PATIENTS AT RISK FOR RHEUMATOID ARTHRITIS: A META-ANALYSIS

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Background: The identification of patients with rheumatoid arthritis (RA) in the early stages of the disease leads to early treatment and improved outcomes. MSUS is a relatively easy, accessible and low cost method, which has been proven more sensitive in detecting findings suggestive of inflammatory arthritis than clinical or radiographic exams. Evidence shows that MSUS seems to bring additional knowledge when assessing the joints on patients with suspected RA, however, there is still controversy whether it can improve substantial discriminatory value for early arthritis.

Objectives: To assess the diagnostic value of MSUS and optimal cutoff criteria for the diagnosis of RA in patients with arthralgia and non-classified arthritis.

Methods: We conducted a meta-analysis for original studies evaluating ultrasound on patients with arthralgias and non-classified arthritis, published in Pubmed, EMBASE and Cochrane databases until December 2017. Statistical analysis included i) the calculation of sensitivity and specificity for ultrasound ii) summary receiver operating characteristic (SROC) curves for a linear regression model iii) I squared test for heterogeneity.

Results: Sixteen studies were included in the review. The overall sensitivity and specificity were 0.75 (95% CI 0.62, 0.88) and 0.72 (95% CI 0.60, 0.83) respectively. The overall diagnostic odds ratio (DOR) was 11.45 (95% CI 6.52, 20.11). The relative DOR for studies performed in Asia (10.43, p=0.002), published before 2013 (15.71, p=0.001) and involving MCP (11.27, p=0.003) and MTP (2.78,