accumulating data now highlight an overlap between these risk loci and cell-specific enhancer elements that is maximal in CD4+ lymphocytes, followed by B lymphocytes

Objectives: Seeking insight into genetic risk mechanisms, we conducted and compared expression quantitative trait locus (eQTL) analyses of risk loci in CD4+ T cells and B cells from carefully phenotyped early arthritis patients naïve to therapeutic immunomodulation.

Methods: 254 patients donated RNA and DNA from purified B and/or CD4+ T-cells within 4 hours of blood draw. Genotyping and global gene expression measurement were carried out using the Illumina Human CoreExome array and either HT12v4 or WG6v3 BeadChip arrays respectively. Variants in linkage disequilibrium (LD) with 101 confirmed non-HLA RA- SNPs ($r^2>0.8$) were analysed, seeking evidence of *cis*- or *trans*- eQTLs according to whether associated probes were or were not within 4MB of these LD blocks.

Results: Genes subject to *cis* eQTL effects common to both CD4+ and B-lymphocytes at RA risk loci were *FADS1*, *FADS2*, *BLK*, *FCRL3*, *ORMDL3* and *GSDMB*. At the 8p23 *BLK-FAM167A* locus, we found adjacent genes subject to eQTLs whose activity differed markedly between cell types, the *FAM167A* effect displaying striking B-lymphocyte specificity. By contrast, *cis* eQTLs acting on *METTL21B*, *IKZF3,* and *PADI4* were unique to CD4+ lymphocytes, the latter two of these being identified for the first time in this cell subset. No *trans* eQTLs approached experiment-wide significance, and linear modelling did not identify a significant influence of biological co-variates (diagnosis, systemic inflammation, age) upon eQTL effect sizes.

Conclusions: Our findings refine understanding of candidate causal genes in RA pathogenesis, providing an important platform from which downstream functional studies may be prioritised and directed towards particular cell types.

References:

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THU0004 CROSS PHENOTYPE ASSOCIATION MAPPING OF THE MHC IDENTIFIES GENETIC VARIANTS THAT DIFFERENTIATE PSORIATIC ARTHRITIS FROM PSORIASIS

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Background: The identification of genetic variants that differentiate PsA from psoriasis has the potential to help us understand the underlying biological pathways that lead to the development of PsA. Associations to genetic variants within the major histocompatibility complex (MHC), in particular to *HLA-C*0602*, increase risk of both PsA and psoriasis when compared to control populations. However direct comparisons of PsA to psoriasis have led to paradoxical associations where *HLA-C*0602* has been reported to be protective of PsA. In addition *HLA-C*0602* has been reported to be associated with age of onset of psoriasis. A more recent study has reported the amino acid at position 45 of the HLA-B protein as the most important factor for differentiating PsA from psoriasis.

Objectives: Here we perform a cross phenotype association analysis in an attempt to identify genetic variants in the MHC that differentiate PsA from psoriasis in a large collection of PsA patients and psoriasis patients screened for the absence of PsA.

Methods: A total of 1069 patients with psoriasis and 981 patients with PsA from the UK were genotyped using either the Illumina Immunochip or the Illumina OmniExpress genotyping arrays. SNPs, amino acids and classical HLA alleles were imputed using SNP2HLA. Logistic regression was used to compare the imputed dosage of MHC markers between PsA and psoriasis. All analyses were repeated using age of psoriasis onset as an additional covariate.

Results: The most significant association when comparing PsA to psoriasis was to *HLA-C*0602* ($p=4.17x10^{-15}$) with a protective effect for PsA (OR 0.52, CI 0.44:0.61). *HLA-C*0602* was found to be significantly associated with a younger age of psoriasis onset ($p=1.51x10^{-60}$) where the median age of onset in years for carriage is 22 compared to 33 for non-carriage. We observed a difference in the median age of psoriasis onset in years between the PsA and psoriasis study subgroups (34 vs. 21), highlighting the potential for bias at markers associated with age of psoriasis onset. When controlling for the age of psoriasis onset in the analyses we observed no association of PsA to *HLA-C*0602* (p=0.07) and the most significant association was to the amino acid at position 97 of HLA-B ($p=1.54x10^{-9}$) where the presence of asparagine or serine residue increased risk of PsA. Asparagine at position 97 of HLA-B defines the HLA-B*2705 allele.

Conclusions: Comparing PsA to psoriasis we show *HLA-C*0602* confers no effect, either risk or protective, for PsA after correction for age of psoriasis onset. The results suggest that the previously observed protective effect of *HLA-C*0602* could be due to confounding due to a younger age of psoriasis onset in the psoriasis subgroup. When accounting for age of psoriasis onset, the primary association conferring risk for PsA in patients with psoriasis is to HLA-B amino-acid 97 where an asparagine residue defines the *HLA-B*2705* allele. In addition, this amino acid has been reported as the largest genetic effect for ankylosing spondylitis thereby refining the genetic overlap between these two spondyloarthropathies.

Disclosure of Interest: None declared

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THU0005 ERAP POLYMORPHISMS AND ITS ASSOCIATION WITH HLA-B15 AND HLA-B27 POSITIVE SPONDYLARTHRITIS PATIENTS

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Background: Since 1973, the association of HLA-B27 and spondyloarthritis (SpA) is well known, however in Colombian population it is present in only 40% of patients and HLA-B15 is present almost in 25%. A mechanism of polygenic mechanism has been proposed as an explanation for the development of SpA. Endoplasmic reticulum aminopeptidase (ERAP) genes 1 and 2 have been implicated. ERAP1 is strongly associated with HLA-B27 positive patients and ankylosing spondylitis, but not with ERAP2

Objectives: To determine the association between ERAP polymorphisms and HLA-B27 or HLA-B15 positive SpA patients

Methods: 178 patients with SpA according to ASAS criteria were included in the study. HLA typing was performed by the PCR technique using the Biorad® HLA-SSP plates. The polymorphisms were determined by the RT-PCR technique using Roche® probes for ERAP1 rs27044, rs17482078, rs10050860, and rs30187. For ERAP2 the probes used were rs2910686, rs2248374 and rs2549782. The

Table 1. ERAP2 Haplotypes in HLA-B15 and B27 Patients

Haplotypes	HLA B15 n (AF)	HLA B27 n (AF)	OR (CI 95%)	*p*
TGT	**0.201**	0.078	2.943 (1.264–6.585)	0.009*
TGC	0.055	**0.227**	4.483 (1.524–13.187)	0.003*
CAT	0.021	**0.119**	9.014 (1.181–68.807)	0.009*
CAC	0.643	0.499	1.750 (0.968–3.162)	0.077
CGC	0.016	0.035	0.465 (0.053–4.056)	0.672
CGT	0.031	0.013	2.406 (0.332–17.45)	0.584
TAT	0.019	0.013	1.185 (0.106–13.29)	1.00
TAC	0.013	0.015	1.185 (0.106–13.29)	1.00

ERAP: endoplasmic reticulum aminopeptidase; AF: allelic frequency; OR: odds ratio.

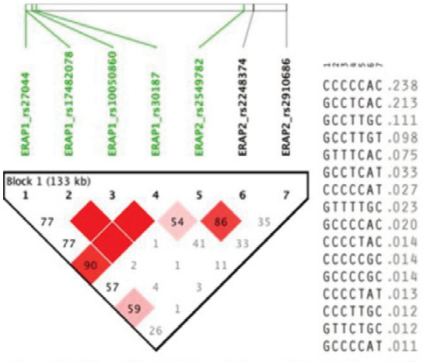

Figure 1. Linkage disequilibrium (LD) map of the ERAP gene. The value of the LD coefficient in each cell D'[(values close to 1.0) x 100] is shown. The colour map of the haplogroups represents the LD relationships, the bright red squares represent evidence of LD (log odds [LOD] score <2 and D'= 1], the light red squares indicate a slight evidence of LD (log odds [LOD] score≥2 and D'<1], and white squares mean that there is no LD and independent segregation [log odds [LOD] score<2 and D'<1]

allele and genotype frequencies polymorphisms were obtained by direct counting. In each group the Hardy-Weinberg equilibrium was evaluated using the ^{2} test. Associations were assessed using odds ratio (OR). Stata v.12.0 program was used to analyse data. The construction and analysis of haplotypes was performed using Haploview v.4.2

Results: In total 70 patients were HLA-B27 positive and 34 were HLA-B15 positive. 78 were women and 100 were men. Linkage disequilibrium map of the ERAP gene is depicted in figure 1. When analysed by ERAP2 haplotype it is observed that there is a statistically significant association with the combinations described in table 1. No associations were observed between ERAP1 haplotypes and HLA-B15 or B27

Conclusions: In the group of patients analysed, a statistically significant association was found between patients with SpA HLA-B15 positive and the haplotype TGT of ERAP2. Also HLA-B27 positive SpA patients were associated with haplotype TGC and CAT of ERAP2 with statistical significance

Disclosure of Interest: None declared

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THU0006 TRANS-ETHNIC META-ANALYSIS OF GENOME-WIDE ASSOCIATION STUDIES IDENTIFIES GSDMA AND PRDM1 AS SUSCEPTIBILITY GENES TO SYSTEMIC SCLEROSIS

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Background: Systemic sclerosis (SSc) is an autoimmune disease characterized by fibrosis and composed of two subtypes, limited and diffuse cutaneous forms. Previous genetic studies including genome-wide association studies (GWAS) have identified 12 susceptibility loci satisfying genome-wide significance.

Objectives: To expand the list of susceptibility genes and deepen biological insights for SSc.

Methods: We performed trans-ethnic meta-analysis of GWAS in the Japanese and European populations, followed by a two-staged replication study comprising a total of 4,436 cases and 14,751 controls. Associations between significant single nuclear polymorphisms (SNPs) and neighboring genes were evaluated. Enrichment analysis of H3K4Me3, a representative histone mark for active promoter was conducted with an expanded list of SSc susceptibility genes.

Results: We identified two significant SNP in two loci, *GSDMA* and *PRDM1*, both of which are related with immune functions and associated with other autoimmune diseases ($p=1.4x10^{-10}$ and $6.6x10^{-10}$, respectively). *GSDMA* also showed a significant association with limited cutaneous SSc. We also replicated the associations of previously reported loci including a non-GWAS locus, *TNFAIP3*. *PRDM1* encodes BLIMP1, a transcription factor regulating T cell proliferation and plasma cell differentiation. The top SNP in *GSDMA* was a missense variant and correlated with gene expression of neighboring genes, and this could explain the association in this locus. We found different HLA association patterns between the two populations or two subtypes. Enrichment analysis suggested the importance of CD4 naïve primary T cell.

Conclusions: *GSDMA* and *PRDM1* are associated with SSc. These findings provide enhanced insight into the genetic and biological basis of SSc.

Disclosure of Interest: None declared

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THU0007 DEEP SEQUENCING TRANSCRIPTOME ANALYSIS OF THE EFFECT OF TRAUMEEL VERSUS DICLOFENAC THERAPEUTIC ACTION IN WOUND HEALING

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Background: Anti-inflammatory agents are used widely in treating numerous inflammatory conditions. The effect of Tr14, a multitargeted natural product, was compared to diclofenac, a non-selective cyclooxygenase inhibitor, on cutaneous wound repair in mice.

Objectives: To compare the effect of diclofenac with Tr14 on the transcriptome after cutaneous wounding in the mouse.

Methods: After abrasive wounding, the wounds were treated with topical Tr14 or diclofenac at clinically relevant doses. An additional group received subcutaneous Tr14 injections. The healing wounds were analyzed for RNA transcript profiling by RNAseq at specific times (12h, 24h, 36h, 72h, 96h, 120h, 196h) after injury. Differentially expressed genes (DEGs) were computed at each time point between diclofenac vs control or Tr14 vs control using EdgeR.

Results: Across time points, Tr14 treatment modulated a number of transcripts related to key wound repair pathways such as cellular differentiation, wound contraction, and cell mobility. Diclofenac, in contrast, changed gene expression mainly in two areas: Prominent effects were observed with regard to DNA chromatin regulation and ribosomal function, further effects were observed on the prostaglandin pathway and wound repair factors. In many of the key pathways modulated by Tr14, such as the defense response and cell motility, diclofenac tended to have an opposite effect on gene expression. At 12 hours post-injury, there were 521 transcripts significantly elevated and 1027 transcripts that were decreased by diclofenac treatment. By comparison, using a similar number of transcripts altered by Tr14 treatment, only 4 transcripts were increased in common, and 5 transcripts were decreased in common, suggesting that the therapies have different effects on the transcriptome.

Conclusions: The overall patterns of the Tr14 and diclofenac responses in the transcriptome during wound repair are very different. The Tr14 effect is most pronounced on the defense response, cell motility, and anti-apoptotic pathways. In contrast, diclofenac mainly affected histones and chromatin remodeling systems, as well as ribosomal systems that would be expected to alter the translational pattern of diclofenac-treated cells.

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THU0008 MAST CELLS SHOW A REPROGRAMMED TRANSCRIPTIONAL SIGNATURE FOLLOWING REPEATED IGG STIMULATIONS

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Background: Mast cell numbers are increased in the rheumatoid arthritis joint. We have previously shown that mast cells can be activated by IgG-ACPA leading to the production of proinflammatory cytokines. However, not much is known about the resulting function when mast cells would repeatedly engage IgG, a likely scenario given the long life span of mast cells (up to a year) and the perpetual presence of IgG-ACPA in the joints. We have recently shown that mast cells triggered repeatedly through their Ig Fc epsilon receptor undergo a reprogramming of their responses (*Suurmond et al. JACI, 2016* by expressing de-novo transcribed genes in the antigen presentation and pathogen defence response pathways.

Objectives: The aim of the current work was to determine whether mast cells show similar changes in their response mode following repeated interactions with IgG.

Methods: Human cord blood-derived mast cells were treated for 2 weeks with plate-bound IgG. The expression profile of naive or treated mast cells was measured through RNA sequencing, quantitative RT-PCR, flow cytometry. Protein secretion was measured with ELISA and Luminex assays. Metabolic changes were measured using HPLC mass-spectrometry.

Results: Similar to our previous work on Fc Epsilon receptor, we observe a dampening of the normal IgG responses with a set of novel genes upregulated. Interestingly, de-novo expressed genes consisted of *DHCR7* and *DHCR24*, key enzymes in the cholesterol pathway. Pathway analysis confirms an enrichment of genes in this pathway following repeated IgG triggering. Preliminary data on metabolic profiling reveals a decrease in phospholipid levels in repeatedly activated mast cells.

Conclusions: Our study provides evidence that mast cells are reprogrammed upon repeated IgG triggering. In contrast to repeated Fc Epsilon Receptor triggering, different pathways are affected, implying stimulus-specific effects. Our work has important implications for the understanding the role of mast cells in rheumatoid arthritis.