Background: To date more than 100 genetic loci have been associated with rheumatoid arthritis (RA), particularly in the human leukocyte antigen (HLA) region. Our understanding of the functional consequences of genetic variation in RA causality, however, is limited and it has been shown that a substantial portion of complex disease risk alleles modify gene expression in a cell-specific manner [1]. The Pathobiology of Early Arthritis Cohort (PEAC) is a longitudinal study looking at treatment-naïve RA patients with genotyped data as well as both synovial and blood RNA-sequenced biopsies prior to treatment with disease modifying anti-rheumatic drugs (DMARDs).

Objectives: To explore expression quantitative trait loci (eQTL) in synovium and blood within PEAC and characterise the effects of genetic variation on gene expression measured by RNA-sequencing. A further goal was to investigate the role of these variants in RA disease severity and response variables.

Methods: Genotypes were generated by Illumina Human CoreExome-24 version 1-0 array in 118 RA patients. Single nucleotide polymorphisms (SNPs) in the HLA region were imputed using HLA-TAPAS. A candidate gene study was performed on variants within the HLA region using Plink v2.0. Synovial (n=85) and blood (n=51) RNA-sequenced samples then underwent cis-eQTL analysis (loci within ±5x10^5Mb of the variant) based on linear regression models with the matrixeQTL R package using PEER [2] and PCA eigenvectors as covariates. Differences in eQTL between tissues were determined using a linear interaction term.

Results: The candidate gene study determined several amino acids around HLA-DRB1 acting as markers for seropositivity, which replicated findings by Raychaudhuri et. al. [3]. Using eQTL analysis, around 33,000 synovial SNPs were found with genome-wide significance (p ≤ 5x10^-8) and around 29,000 in blood. This corresponded to 279 unique significant genes in synovium and 417 in blood (Figure 1). There were 100 genes common to both synovium and blood, including PSORS1C3, HLA-DRB9 and ERAP2, which have known associations with autoimmune diseases and inflammatory arthritis. Notably, 92 genes showed significantly different patterns of QTL expression between synovial tissue and blood (p ≤ 5x10^-8), eQTL data also confirmed the triad of genetic variants significantly driving tissue gene expression of HLA-DBP2, while both HLA-DBP2 SNPs and HLA-DBP2 RNA-sequencing synovial expression correlated highly with erythrocyte sedimentation rate (ESR).

Figure 1. Three class Venn diagram of the genomic grammar between RA, MS and SLE.

Conclusion: The identification of the optimal genomic grammar in RA will help towards understanding the nature of the disease. Specific genetic targets via determined SNPs could act as biomarkers that aid in forming the right diagnosis [6].

REFERENCES:

Disclosure of Interests: None declared.

Conclusion: The high significance of genes in the HLA region in both tissues is inkeeping with the strong association between HLA and susceptibility to RA, as well as other autoimmune diseases. Most notably variants linked to HLA-DPB2 survive expression screening, and are found to be a marker for organ-specific involvement among SLE patients. Additionally, the significant differences between eQTL in blood and synovium highlight the need to explore functional consequences of genetic associations in the diseased tissue directly.

REFERENCES:
[1] Thalassiosirin et al. (2018). CD4+ and B lymphocyte expression quantitative trait loci (eQTL) analysis for 85 synovial samples (top) and 51 blood samples (middle). Tissue interaction eQTL (bottom) show significant differences between tissues (p ≤ 5×10^-7).

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Figure 1. Manhattan plots for cis-expression quantitative trait loci (eQTL) analysis performed on 85 synovial samples (top) and 51 blood samples (middle). Tissue interaction eQTL (bottom) show significant differences between tissues (p ≤ 5×10^-7).

Moreover, we demonstrated cell-type-specific contributions to diverse organ involvement, e.g., Th1 for mucocutaneous, monocyte-lineage cells for muscle-skeletal, neutrophil-lineage cells for renal activity, respectively. We also observed the strong associations of disease-activity signatures with treatment effect: (i) belimumab suppressed activity signatures from B-lineage cells, especially in good responders and (ii) mycophenolate mofetil substantially suppressed activity signatures from plasmablast, Th1, and central memory CD8+ cells. However, through stratified LD score regression using large-scale SLE-GWASs, we revealed that disease-activity signatures were less enriched around SLE risk variants than disease-state signatures. Consistent with this result, the directions of SLE risk alleles’ expression quantitative trait locus (eQTL) effects were significantly concordant with the directions of disease-state signatures, but not with those of activity signatures. These findings suggested that the current genetic case-control studies may not well capture clinically vital biology linked to drug target discovery for SLE. Meanwhile, we also detected some examples of activity signatures that might contribute to the disease risk by modulating risk allele’s eQTL effects.

Figure 1. Manhattan plots for cis-expression quantitative trait loci (eQTL) analysis performed on 85 synovial samples (top) and 51 blood samples (middle). Tissue interaction eQTL (bottom) show significant differences between tissues (p ≤ 5×10^-7).

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