Methods: CD4+ and CD8+ T cells were isolated from peripheral blood from 10 healthy controls and 48 PsA patients and from 6 PsA synovial fluid samples. We performed RNA-seq and ATAC-seq on these two cell types to analyse the global patterns of gene expression and chromatin activity.

Results: We find subtle differences between PsA patients and healthy controls in cells isolated from blood. RNA-seq analysis identified only a handful of differentially expressed genes whilst ATAC-seq analysis identified only 28 differential loci. On the other hand, T cells isolated from synovial fluid showed significant differences compared to T cells isolated from patient’s blood. Interestingly, we find that CD4+ T cells show substantially more differentially expressed genes compared to CD8+ T cells (1168 vs 346 Log2FoldChange > 1, FDR < 0.01). Genes overexpressed in synovial CD4+ T cells are more strongly enriched for immune pathways such as cytokine signaling and T cell proliferation compared to synovial CD8+ T cells.

We also find that synovial CD4+ T cells highly overexpress MHC class II genes (Figure 1).

Conclusion: This preliminary analysis suggests that T cells isolated from peripheral blood do not seem to differ significantly between PsA patients and healthy controls. In contrast, cells isolated from synovial fluid are highly specialized and activated. Moreover, these cells do not resemble canonically activated T cells which means that this state cannot be easily emulated in vitro. This study indicates the importance of not only studying GWAS loci in relevant primary cells from patients, but also that attention needs to be given to cells isolated from the affected site.

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POS0036 CORRELATION BETWEEN SYSTEMIC AND LOCAL EXPRESSION LEVELS OF MIR-146A, MIR-155 AND MIR-223 AND THE ONGOING TREATMENT IN RHEUMATOID ARTHRITIS PATIENTS

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Background: MicroRNAs (miRNAs) comprise a class of small, non-coding RNAs that serve as important negative regulators of gene expression at posttranscriptional level. Studies have shown that dysregulation of miRNA expression in autoimmune diseases, such as rheumatoid arthritis (RA) which makes them a potential systemic as well as local biomarkers for disease activity (1-3). On the other hand, regulation of miRNA on transcriptional and posttranscriptional level, as well as the effects of endogenous and exogenous factors on miRNA expression is under investigation. Of importance is the possible effect of the ongoing treatment on miRNA expression in the clinical practice.

Objectives: To analyze the expression levels of miR-146a, miR-155 and miR-223 in peripheral blood (PB) and synovial fluid (SF) from RA patients in regard to the ongoing treatment regimen.

Methods: A total number of 63 RA patients according to the 1987 ACR criteria were included in the study. Expression levels of miR-146a, miR-155 and miR-223 in 63 PB samples and matched 48 SF samples were determined by qPCR (SyBrGreen technology) and compared to healthy controls (HCs). Relative changes of gene expression levels of the studied miRNAs were calculated by 2-ΔΔCT method. 45 of the studied patients were on systemic treatment, which included non-steroidal antiinflammatory drugs (NSAIDs), glucocorticosteroids (GCS), conventional synthetic disease-modifying antirheumatic drugs (cDMARDs) and original biological DMARDs. There were no patients treated with conventional target DMARDs or biosimilar DMARDs. SPSS was used for statistical analysis.

Results: RA PB showed statistically significant overexpression of miR-223 (58.73%) when compared to HCs and only miR-223 expression levels could be used to differentiate RA patients from HCs (p=0.008). RA SF showed overexpression of miR-146a (in 70.83%, p=0.007), miR-155 (in 71.79%, p=1.63x10^-10) and of miR-223 (in 71.79%, p=1.64x10^-7) when compared to HCs and the studied miRNAs could be used to differentiate RA patients from HCs (p=4.8x10^-5, p=8.03x10^-5 and p=2.8x10^-7, respectively). When we analyzed the correlation between the expression of miRNAs and the ongoing treatment we found a statistically significant correlation between the PB expression levels of miR-223 and the use of NSAIDs and GCS (p=0.015 and p=0.04, respectively) and the SF expression levels of miR-146a and miR-155 and the use of NSAIDs (p=0.011 and 7.98x10^-6, respectively) and GCS (p=0.039 and p=0.009, respectively). The use of cDMARDs and bDMARDs didn’t show correlation with the PB nor the SF expression of the studied miRNAs.

Conclusion: The correlation between the systemic miR-223 and the local miR-146a and miR-155 expression with the NSAIDs and GCS treatment could be due to the effect of these treatment compounds on the cells lines from which the studied miRNAs origin. In our study there was no correlation between miRNA expression and the use of biological and conventional DMARDs. Further analysis with larger sets including pre- and posttreatment samples is needed to confirm if altered miRNA expression could be influenced by the treatment regimen as well as if miRNAs could serve as biomarkers for treatment response in the clinical practice.

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POS0037 MULTIVARIATE MENDELIAN RANDOMIZATION STUDY ON BMI-ADJUSTED LINK BETWEEN ADIPONECTIN AND RISK OF DEVELOPING RHEUMATOID ARTHRITIS

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Background: Compelling evidence suggests that adiponectin is involved in the pathogenesis of rheumatoid arthritis (RA). Nevertheless, a recent Mendelian randomization (MR) study in Europeans has shown that adiponectin does not have a causal role in the development of RA1.

Objectives: As body-mass index (BMI) is a known risk factor for RA2 and subjects with high BMI have lower circulating levels of adiponectin, we specifically aimed to perform a multivariable MR in both European and East Asian populations to determine if adiponectin has a causal effect on RA development independently of BMI.

Methods: We performed a range of two-sample, univariable, MR analyses to assess the causal effect of adiponectin on RA in European and East Asian individuals. Two different sets (12 in Europeans and 5 in East Asians) of adiponectin-related genetic variants were used as instruments for genetically determined adiponectin levels, to calculate its causal effect on RA risk. Multivariable MR was performed to calculate the effect of adiponectin on RA risk after adjustment for BMI.

Results: Univariable MR did not provide evidence of a causal relationship between circulating adiponectin levels and RA risk in both European (OR 1.06; 95% CI 0.87-1.31; p=0.59) and East Asian (OR 1.04; 95% CI 0.91 – 1.19; p=0.54) individuals (Figure 1). Similarly, there was no evidence of a causal effect of
genes (n total=162) among genes annotated to VTE significant GWA loci.

Objectives: The objective of this study is to clarify the putative genomic vulner-
ability to dysregulated JAK-STAT signaling in VTE.

Methods: We are systematically mine and analyze large-scale genomic datasets
generated from studies comparing VTE patients with healthy controls. Using VTE
genome-wide associated (GWA) summary statistics we evaluate the representa-
tion of genes encoding the JAK-STAT pathway (KEGG hsa04630) in associated
traits and assess their association to VTE. Further, we examine the genetic VTE
risk burden in the chromatin interactome of STAT family transcription factors
(TFs). We extract available STAT family (STAT-1-3) TF binding site (TFBSs)
census DNA motifs (JASPAR database) and assess the association of genes containing
STAT family TFBSs within their promoter sequence (TSS –2000bp) to VTE. Through mining of deposited OMICs data from VTE patients, we exam-
ie molecular characteristics related to JAK-STAT signaling, including potential
enrichment of STAT family TFBSs among query promoter sequences of differ-
ently expressed genes (DEGs).

Results: We do not observe a significant overrepresentation of JAK-STAT
genes (n overlap=162) among genes annotated to VTE significant GWA loci
(n total=147, p=0.48). Similarly, the JAK-STAT gene set show no cumulative
association to VTE (p=0.98). Applying the same gene set association approach to
the STAT target gene sets (n total=4570) does not reveal significant associ-
ation between VTE and STAT1 (n overlap=10, p=0.47), STAT1:STAT2 heterodi-
mers (n overlap=18, p=0.17) and STAT3 (n overlap=48, p=0.20) target gene sets. At
the functional molecular level, we do not see any significant overlap between
molecules acting in the JAK-STAT pathway and DEGs (n overlap=507, p=0.06) or
differentially abundant proteins (DAPs; n overlap=35, p=0.57). However, we observe
a significant overlap between downregulated DEGs (n overlap=362) and the
STAT1:STAT2 heterodimer target gene set (n overlap=2155, p=0.0001)
including downregulation of IL-27RA and CCND3 (Figure 1). Supporting the
biological relevance of this finding, we find a weak but statistically significant
enrichment of STAT1 TFBS motifs in the promoter sequence of downregulated
DEGs compared to non-DEGs (p=0.02).

Conclusion: This MR study does not support a causal effect of genetically
determined adiponectin levels on the risk of developing RA in both European
and East Asian populations. By using multivariable MR to account for possible
shared genetic predictors between circulating adiponectin levels and BMI we
have shown that circulating adiponectin is not causally linked to RA risk after
adjustment for BMI.

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POSO038 GENOMICS OF JAK-STAT SIGNALING IN VENOUS
THROMBOEMBOLISM
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Background: Janus kinase inhibitors (JAKi) have been associated with an
increased risk of venous thromboembolism (VTE) [1]. VTE comprises deep vein
thrombosis and pulmonary embolism and is associated with complications such
as recurrent VTE, post thrombotic syndrome, pulmonary hypertension, and
death. These concerns limit the use of JAKi-based therapy. To improve risk stratifi-
cation and drug development, it is crucial to understand the possible implication
of dysregulated JAK-signal transducers and activators of transcription (STAT)
signaling in the pathogenesis of VTE

Objectives: The objective of this study is to clarify the putative genomic vulner-
ability to dysregulated JAK-STAT signaling in VTE.

Methods: We are systematically mine and analyze large-scale genomic datasets
generated from studies comparing VTE patients with healthy controls. Using VTE
genome-wide associated (GWA) summary statistics we evaluate the representa-
tion of genes encoding the JAK-STAT pathway (KEGG hsa04630) in associated
traits and assess their association to VTE. Further, we examine the genetic VTE
risk burden in the chromatin interactome of STAT family transcription factors
(TFs). We extract available STAT family (STAT-1-3) TF binding site (TFBSs)
census DNA motifs (JASPAR database) and assess the association of genes containing
STAT family TFBSs within their promoter sequence (TSS –2000bp) to VTE. Through mining of deposited OMICs data from VTE patients, we exam-
ie molecular characteristics related to JAK-STAT signaling, including potential
enrichment of STAT family TFBSs among query promoter sequences of differ-
ently expressed genes (DEGs).

Results: We do not observe a significant overrepresentation of JAK-STAT
genes (n overlap=162) among genes annotated to VTE significant GWA loci
(n total=147, p=0.48). Similarly, the JAK-STAT gene set show no cumulative
association to VTE (p=0.98). Applying the same gene set association approach to
the STAT target gene sets (n total=4570) does not reveal significant associ-
ation between VTE and STAT1 (n overlap=10, p=0.47), STAT1:STAT2 heterodi-
mers (n overlap=18, p=0.17) and STAT3 (n overlap=48, p=0.20) target gene sets. At
the functional molecular level, we do not see any significant overlap between
molecules acting in the JAK-STAT pathway and DEGs (n overlap=507, p=0.06) or
differentially abundant proteins (DAPs; n overlap=35, p=0.57). However, we observe
a significant overlap between downregulated DEGs (n overlap=362) and the
STAT1:STAT2 heterodimer target gene set (n overlap=2155, p=0.0001)
including downregulation of IL-27RA and CCND3 (Figure 1). Supporting the
biological relevance of this finding, we find a weak but statistically significant
enrichment of STAT1 TFBS motifs in the promoter sequence of downregulated
DEGs compared to non-DEGs (p=0.02).

Conclusion: Here, we provide a coherent approach to assess the genomic basis
for the reported association between JAKi treatment and VTE. Our preliminary
data suggest that genes under transcriptional control of STAT family TFs may
be dysregulated in VTE patients. It is conceivable, that the genomic actions of
JAKi is overlapping with the molecular risk profile of VTE. CCND3 is especially
interesting because VTE occurs in up to 10% of patients treated with cyclin-de-
pendent kinase inhibitors such as Palbociclib [1]. Obviously, genomic data mining
alone cannot guide medical decision making concerning the use of JAKi. How-
ever, our results provide a basis for further investigation of adverse events seen
with JAKi.

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POSO039 MONOCYTE TRANSCRIPTOMICS AND TARGETED
PROTEOMICS DEFINE HETEROGENEOUS
SUBGROUPS IN WOMEN WITH SYSTEMIC LUPUS
ERYTHEMATOSUS (SLE) AND SUBCLINICAL
ATHEROSCLEROSIS
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Figure 1. Forest plot of the causal effects of adiponectin-associated genetic variants on rheu-
matoid arthritis after adjustment for body mass index in a multivariable mendelian randomiza-
tion (MR) analysis. Shown are European (EUR) and East Asian (EAS) populations. An Odds
Ratio (OR) is a measure of association between an exposure and an outcome, in which the
OR represents the likelihood that an outcome will occur given a particular exposure, compared
to the likelihood of the outcome occurring in the absence of that exposure. Statistical analyses
were performed with the use of inverse-variance-weighted (IVW) estimate, MR-Egger regres-
sion weighted median analysis.

Conclusion: This MR study does not support a causal effect of genetically
determined adiponectin levels on the risk of developing RA in both European
and East Asian populations. By using multivariable MR to account for possible
shared genetic predictors between circulating adiponectin levels and BMI we
have shown that circulating adiponectin is not causally linked to RA risk after
adjustment for BMI.