Transcriptomics

**LUPUS AUTOANTIBODIES ASSOCIATED WITH CELL CYCLE GENE EXPRESSION IN PERIPHERAL BLOOD OF SLE PATIENTS**

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**Background** Gene-expression studies of SLE peripheral blood indicate the expression of relevant categories of functionally related transcripts. The most pronounced changes have been reported among interferon-inducible genes, genes specific to neutrophil granules and genes involved in cell cycle. Although autoantibodies are considered to be the main pathogenic mediators in SLE, there is little knowledge regarding how their titer is associated with peripheral blood gene expression. To gain insight into mechanisms of autoimmunity, we simultaneously investigated the presence of classical SLE autoantibodies (ANA, dsDNA, Sm/RNP, Ro, La) and gene expression in a cohort of 80 SLE patients followed from 1 to 14 visits over a period of 3(0-12) years.

**Methods** All blood samples were collected at HSS and processed within 1 hour using the same protocol. Gene expression was studied either by RNA-seq (62 samples) or DNA microarray (189 samples) and then merged into a single matrix using the MatchMixeR software. The obtained matrix was used to generate functionally annotated groups of co-expressed genes, also known as gene-modules, using the WGCNA algorithm. The comparison of autoantibody titer with gene expression was analyzed by linear mixed model, using either a per module or per gene approach. Several clustering techniques were used to aggregate common genes and investigate the association with clinical and laboratory parameters.

**Results** All studied patients fulfilled ACR criteria for SLE and received standard care at HSS. We excluded samples obtained after treatment with biologics (rituximab, belimumab). Autoantibodies expressed above the normal range were detected in the following frequencies: 90% ANA, 85% dsDNA, 84% Histone, 54% Sm/RNP, 32% Sm, 65% Ro52 (SSA), and 23% La (SSB). A significant negative correlation between the described autoantibodies and level of complement C3 was observed. Based on gene expression, the only significant association was obtained for genes involved in cell division. Among those, the strongest association was demonstrated with anti-dsDNA titer. Among cell cycle related genes, the most significant correlations (p < 10^{-5}) were seen for TK1, AURKB, KIFC1, KIF15, FOXM1, GINS2, NGAPG, CDC45, CDCA5, CCNA1, CCNB1.

**Conclusions** Autoantibodies directed against nucleic acid containing immune complexes are a characteristic trait in SLE. The aberrant expression of TK1 has been previously shown in bone marrow of SLE patients. Cell-cycle related genes were identified earlier in microarray studies of SLE PBMC. However, association of those transcripts with autoantibodies has not been previously described. Abnormal expression of genes related to cell cycle might cause cell cycle arrest, a DNA...
damage response, senescence, and self-destruction. Those cellular events might in turn trigger overproduction of antinuclear antibodies.

Lay Summary

To gain insight into mechanisms of autoimmunity, we simultaneously investigated the presence of classical SLE autoantibodies (ANA, dsDNA, Sm/RNP, Ro, La) and gene expression in a cohort of 80 SLE patients followed longitudinally. We observed a significant association between antinuclear antibodies titers and genes involved in cell division. The aberrant expression of cell-cycle related genes might cause cell cycle arrest, DNA destruction, and enhanced antinuclear antibodies production in SLE.

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2105 UCSF AUTOIMMUNOPROFILER – UNDERSTANDING THE IMMUNOMES OF AUTOIMMUNE DISEASES

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Background

In autoimmune diseases, like Lupus, immune cells are entangled in stimulatory loops and attack otherwise healthy tissues. In AutoImmunoProfiler we strive to map the different configurations of immune cell interactions in tissues of patients with autoimmune diseases. Overall goals include better understanding of underlying mechanisms of autoimmune diseases, identification of the relationship between tissue and peripheral compartment, and the identification of novel pathways and targets for future drug discovery and development.

Methods

In AutoImmunoProfiler, the UCSF team will initially prospectively collect tissue and blood samples from patients with the following autoimmune diseases: Systemic Lupus Erythematosus (SLE), Scleroderma (SSc), primary Sjögren’s Syndrome (pSS), Ulcerative Colitis (UC), Crohn’s Disease (CD), and Type 1 Diabetes (T1D), and will be complemented by samples from matched healthy controls (HC). Samples are processed and analyzed with the expertise of the UCSF CoLabs, performing: scRNAseq, CITeseq, scATACseq, bulk epigenomic assays (EPIC chip), Bulk RNAseq, Image analysis of tissue biopsies, and Organoid assays (only for IBD).

Results

Autoimmunoprofiler is envisioned to be a consortium effort. Eli Lilly and UCSF are the founding partners, with the expectation to engage additional partners in the future. Since our kick-off in 2021, we have begun to profile the range of autoimmune diseases using a combination of proteomic, transcriptomic, epigenomic, and structural analyses. Emphasis will be on freshly collected tissue samples with matched peripheral blood samples from clinically well-annotated patients with autoimmune diseases.

Conclusions

We have started to map the different configurations of immune cell interactions in tissues of patients with autoimmune diseases. An example of high-resolution data that is being generated in AutoImmunoProfiler is the recent publication in Science “Single-cell RNA-seq reveals cell type-specific