Identification of homogeneous Systemic Lupus Erythematosus (SLE) patient groups using clustered autoantibody reactivities

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Introduction

- The extreme heterogeneity amongst SLE patients is a major obstacle for predicting disease manifestations and for developing effective therapies.

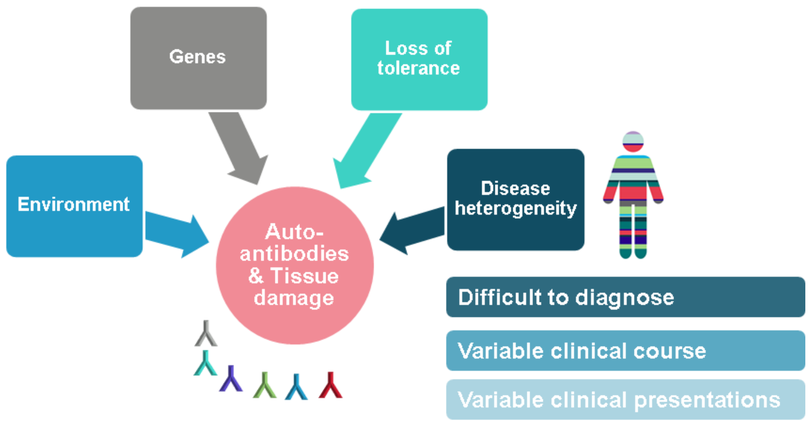

Fig. 1: Serological and clinical heterogeneity of SLE

- Detecting a broad set of autoantibodies (AABs) might help to investigate the number, co-prevalence and similarities of AAB reactivities in SLE patients.
- Here, we describe the development of a multiplexed AAB array enabling the analysis of 87 AABs in SLE patients.

Patients and Methods

We previously reported the discovery and validation of novel SLE-associated autoantibodies using the bead-based Luminex® xMAP® platform SeroTag® [1]. In the current version, SeroTag enables to detect antibodies against 6,912 antigens (well-described and novel) in parallel with small sample volume requirements (25 µl per sample and screen). During discovery and validation studies, AAB reactivity was thoroughly analyzed in 700 SLE, 1,000 healthy control (HC), and 500 autoimmune disease samples (AID) (Fig. 2).

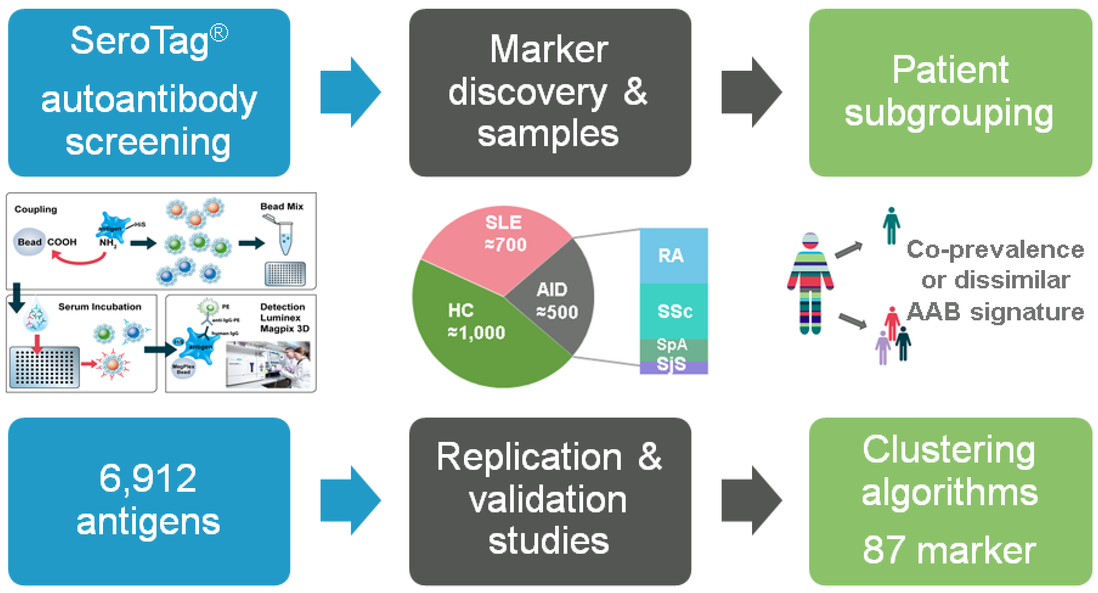

Fig. 2: Discovery and validation of SLE-associated autoantibody marker

Results

Analysis of the identified antigens using the Gene Ontology (GO) Database and STRING (Search Tool for the Retrieval of Interacting Genes/Proteins), revealed that new autoantibodies were found that target proteins involved in apoptotic and immune processes or are encoded by type I interferon response genes (Fig. 3).

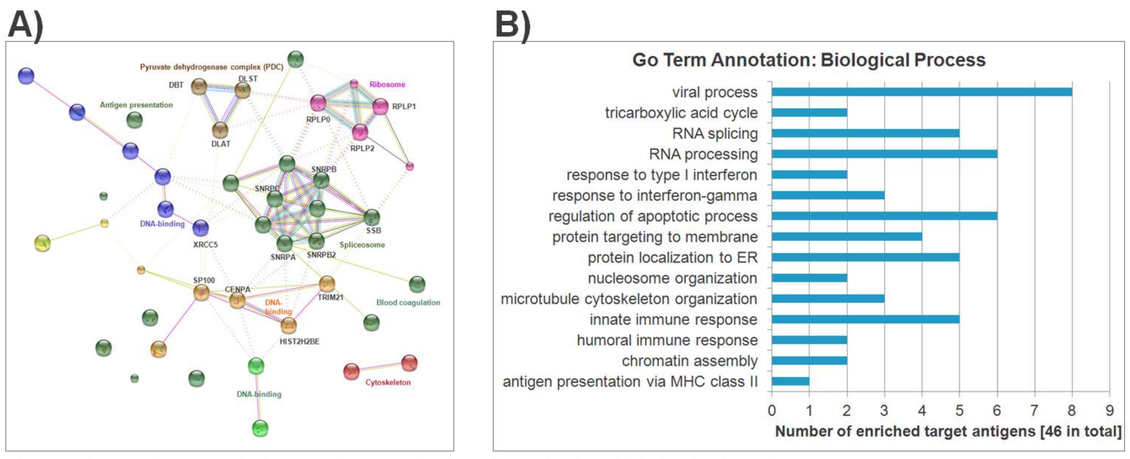

Fig. 3: A) Protein-protein interaction analysis; B) Analysis of biological pathways

SLE Autoantibody Reactivity Signatures

A typical feature of SLE is the production of a broad and heterogeneous group of autoantibodies. Despite efforts to link individual autoantibody reactivities to distinct clinical features, the co-prevalence of AABs in SLE patients has rarely been analyzed. Based on our discovery and validation efforts we designed an SLE stratification assay, which includes new and diagnostic antigens (Fig. 4).

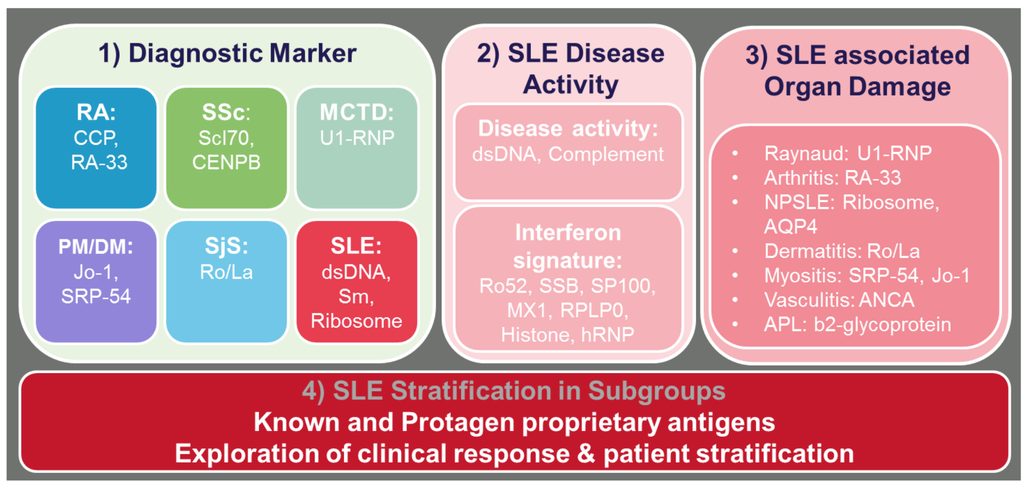

Fig. 4: NavigAID SLE stratification assay

The SLE stratification assay was applied to measure the total number and co-prevalence of autoantibodies in each SLE patient. Fig. 5A shows a contingency heatmap of SLE serum samples in which the total number of AABs present in each sample is shown as a color gradient (from green to red up to 60 AAB). Furthermore, similarities (co-prevalence) and dissimilarities are revealed by plotting two samples against each other. The analysis of the AAB reactivity yields at least four different reactivity groups (G1-G4) including patients: G1: a higher disease activity score, broad and homogeneous AAB reactivity; G2: with broad, but heterogeneous AAB reactivity; G3: who have few AABs and G4: with unusual AAB pattern.

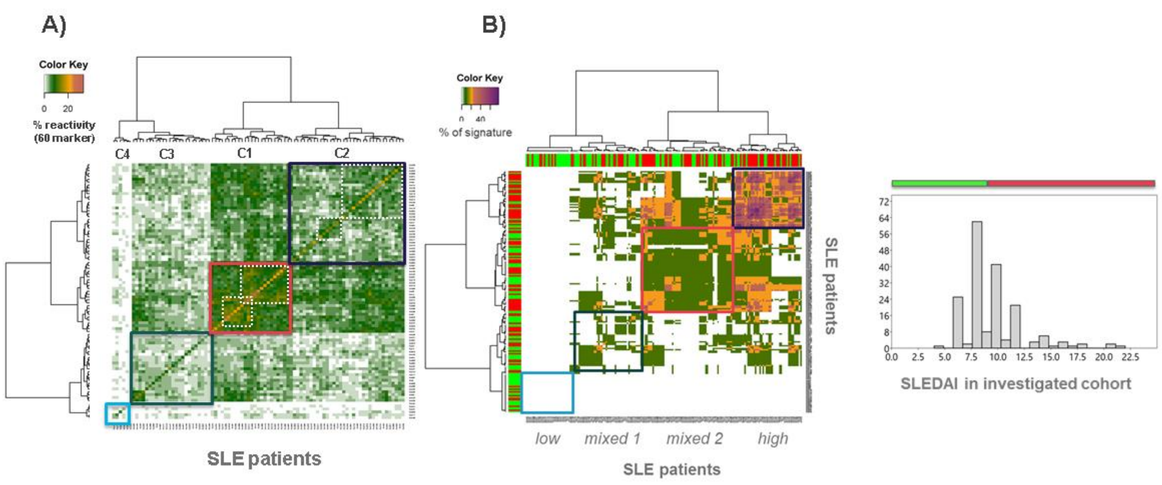

Fig. 5: A) Signature based on all markers B) Signature based on 10 marker that are linked to the INFtype I pathway

Fig. 5B shows the analysis of 10 AABs targeting proteins known to be involved in the INF-type I response pathway. Specific clinical features including more severe disease activity (Systemic Lupus Erythematosus Disease Activity Index, SLEDAI) are associated with high AAB signature reactivity.

Conclusions

The multiplexed analysis of AABs in SLE enables defining an AAB reactivity score and SLE patient clusters. This might support the stratification of SLE patients into more homogenous subgroups in clinical studies thereby increasing the probability of successful drug development.

[1] Budde, P., S. Vordenbäumen, et al. (2015). "SAT0626 Discovery and Validation of New Autoantibody Biomarker in Systemic Lupus erythematosus." Ann Rheum Dis 74(Suppl 2): 888.

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