Identification of Subgroups of Systemic Lupus Erythematosus Patients based on Autoantibody Profiling


Introduction

Systemic lupus erythematosus (SLE) is characterized by extensive immune system aberrations leading to the production of autoantibodies of which many are directed towards nucleic acids (anti-dsDNA) and nuclear protein antigens (ANA). These antibodies potentially contribute to pathological processes affecting skin, kidney, neurological system or heart and lung. The clinical and serological diversity of SLE presents important challenges in the diagnosis of the disease as well as affects the clinical development of new SLE therapeutics.

Luminescence bead-based antigen arrays were employed for in-depth characterization of the autoantibody reactivity of SLE as a source to develop improved diagnostic and patient stratification tests for SLE.

Material and Methods

The SeroTag® technology utilizes the bead-based Luminescence xMAP technology which enables to measure the reactivity of autoantibodies (AABs) to thousands of different antigens in a single step measurement (Fig. 1). The flexible design accelerates rapid and efficient validation of new biomarker candidates.

Study Design

A discovery phase in which 130 SLE samples were profiled against rheumatoid arthritis (RA) and healthy controls (HC) was followed by a verification phase in which 100 SLE samples were re-analyzed and tested against HC and a set of samples from other autoimmune diseases (AID) including systemic sclerosis (SSc), ankylosing spondylitis (SPA) and RA. The results from the discovery and verification phase were combined and 286 unique antigens identified. After applying a double filtering procedure with fold change and p-value, 74 putative diagnostic antigens were identified. Further analysis was carried out to identify putative autoantigens for L. nephritis. In total, 85 L. nephritis antigens were identified of which 23 antigens were found in both studies.

Results

Hierarchical cluster analysis was performed to define natural groupings of antigens and patients. The relative strength of reactivity of each antigen in individual patient samples was shown in a heat map by color intensity (yellow) above the cutoff values (black) (Fig. 3). AAB reactivity to 26 confirmed antigens emerged as six clusters. The percentage of AAB-positive SLE patients relative to HCs is shown in Fig. 4.

Conclusions

Comprehensive profiling of SLE sera enabled the in-depth characterization of the autoantigen repertoire of SLE patients. The combination of established and new antigens significantly increased the sensitivity to diagnose SLE. Based on their autoactivity profile SLE sub-groups were revealed, one cluster included autoantibodies significantly associated with L. nephritis. However, further studies are needed to link the remaining clusters to clinical or drug response profiles.