Multiparametric detection of autoantibodies in Systemic Lupus Erythematosus (SLE) enables definition of SLE Patient Subgroups

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Challenges in the Development of SLE Drugs

Susceptibility Genes

Innate Immune System Defects & INF activation

Environmental Trigger

Auto-antibodies & Tissue damage

Loss of Tolerance (B cells, T cells)

Can we define more homogeneous SLE patient populations using autoantibody marker?
Multiplex NavigAID SLE 86 Antigen Array

**SLE-specific Ag**
- dsDNA
- ribosomal P
- Sm
- Complement
- b2GBPI

**INF I pathway Ag**
- Ro52, SSB
- INF, Mx1
- Histone, SP100, RPLP
- hNRPNA1

**AID Ag**
- SSc: CENPB, Topo1
- RA: CCP
- SjS: Ro/SSA, SSB
- DM: Mi2-antigen
- Myositis: t-RNA synthetases
- U1-snRNP, ANCA, Ku

**Novel SLE Ag**
- MVP, TMPO, NONO, hNRNP, BCAP31, NCF2, IL6, BTBD7, PLVAP, FAF1, NRBF2

**SLE subgroups based on autoantibody reactivity**

- AAB profile A
- AAB profile B
- AAB profile C

- Antigen selection based on discovery and validation in >700 SLE
- Novel antigens associated with innate immune response pathways

From Single Marker to Patient Subgroups

Classical Approach:
Heatmap of single marker

- Quantitative autoantibody information is converted into a binarized matrix (AAB yes/no)
- Number of autoantibodies per patient is calculated
- Patient clustering by similarities and differences in autoantibody reactivity
70% (n=31) of glomerulonephrits have an extended autoantibody portfolio
Heatmap of Autoantibody Reactivity per Cluster

Cluster “red”, shows unique reactivity to ANCA antigens (LYZ, CTSG, ELANE, PRTN3)

In cluster “blue”, the four most frequent autoantibody targets are RPLP0, RPLP2, SmD3 and dsDNA

GLMN splits into 2 clusters with different autoantibody reactivity profile
IFN-Pathway Antigens associated with higher SLEDAI

A subgroup of patients with high disease activity shows similar high AAB reactivity to 10 selected IFN pathway antigens
Summary

High content autoantibody analysis in SLE leads to

- Improved differential diagnosis of disease
- Subgrouping of patients based on
  - Signature reactivity
  - Signature similarity
  - Association with organ damage
  - Association with IFN I biology
  - Disease activity
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