

cells, and plasmablasts (CD19+CD38+++IgD-CD27+CD20-) were assessed by multicolor flow cytometry.

**Results** In pts with SLE, compared to healthy donors was found the higher percentage and abs level of memory B cells (14.4 (12.8–23.3) vs 2.15 (1.05–2.95) and 0.016 (0.007–0.03) vs 0.0025

(0.01–0.007)), the higher percentage of non-switched memory B cells (11 (8.7–19.4) vs 7.35 (3.7–11.05)), the higher percentage and abs level of plasmatic cells (2.8 (1.3–4.7) vs 0.1 (0.1–0.2) and 0.002 (0.001–0.006) vs 0.0002 (0.00009–0.0004) and higher percentage and abs level of transitional cells (17.1 (9.0–30.0) vs 0.1 (0.0–0.1) and 0.019 (0.009–0.03) vs 0.0001 (0.0–0.00025)),  $p < 0.05$  for all cases.

In pts with SLE we found a significant correlation between the percentage of CD19+B cells and La-SSB ( $r=0.54$ ), abs memory B cells and La-SSB ( $r=0.53$ ); abs negative correlation between non-switched memory B cells and C3 ( $r=0.67$ ) and C4 ( $r=0.66$ ),  $p < 0.05$  for all cases.

**Conclusions** Patients with SLE showed an increase in the percentage and absolute levels of memory B cells, non-switched memory B cells, plasmatic cells and transitional cells. We found a positive correlation between the B-cell subsets and autoantibody levels and negative correlation with the level of compliment components.

## 7. SLE genetics & omics

### LP-099 HIGH GENETIC RISK LOADS INCREASE THE RISK OF LUPUS NEPHRITIS IN KOREANS

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**Background** Systemic lupus erythematosus (SLE) is an autoimmune disease with heterogeneous manifestations and unpredictable outcome. We aimed to identify the genetic contributions on clinical and serological manifestations in Korean patients with SLE.

**Methods** The patients with SLE were enrolled including a discovery cohort and a replication cohort from the Korean population ( $n = 1,655$ ). Weighted genetic risk score (wGRS) were calculated by SLE risk loci [112 well-validated non-HLA SNPs and HLA-DRB1 haplotype] based on genome-wide association study. Individual wGRS was tested for associations with clinical sub-phenotypes of SLE by using multivariable linear regression or logistic regression.

**Results** Increasing wGRS was significantly associated with more diverse manifestation of SLE, regardless of onset age, sex and disease duration. The SLE patients with high wGRS-quartile were significantly associated with the risk of renal disorder ( $HR=1.74$ ;  $p=2.2 \times 10^{-8}$ ) and anti-Sm antibody production ( $HR=1.85$ ;  $p=2.8 \times 10^{-5}$ ) compared to patients with low wGRS-quartile.

We found that wGRS influenced on the development of proliferative lupus nephritis (LN) [class III or IV ( $HR=1.98$ ,  $p=1.6 \times 10^{-5}$ )] and membranous LN [class V ( $HR=2.79$ ,  $p=1.0 \times 10^{-3}$ )]. Moreover, increasing wGRS had the strongest effect on the development of LN class V in anti-Sm positive SLE ( $AUC=0.681$ ,  $p=1.8 \times 10^{-4}$ ).

**Conclusions** The higher wGRS, which implicated in pathogenesis of SLE, increased the risk to develop lupus nephritis and anti-Sm antibody production. Our study provided that genetic risk loads could predict the clinical outcome in SLE.

### LP-102 UNDERSTANDING HUMAN DISEASE MUTATIONS THROUGH GENE EDITING AND GENOME-WIDE NEXT GENERATION INVESTIGATIONS

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**Background** Mutations, both activating and inactivating ones, continue to be identified in human diseases, including systemic lupus erythematosus (SLE). One emphasis is on mutations in transcription factors and their impact on the genome, leading to disease. Here I discuss experimental approaches, genome-editing coupled with next-generation sequencing-based technologies, that provide a framework to provide insight into the function of mutant proteins in disease. The JAK/STAT (Janus kinase/Signal Transducer and Activator of Transcription) signaling cascade transduces cytokine signals in normal development and disease. Dysregulation of cytokine action on immune cells plays a key role in the initiation and progression of autoimmune diseases including systemic lupus erythematosus (SLE). Elevated levels of phosphorylated (activated) STAT5 are detected in conventional CD4 T cells and activated regulatory T cells of SLE patients. However, the contribution of protein-altering mutations in STAT5 in the etiology of the disease have not been investigated. Mutations in the SH2 domain of STAT5B, which is essential for its dimerization and biological activation, have been identified in patients with T cell leukemias.

**Methods** The Y665F mutation has been identified in patients with T cell large granulocyte lymphocytic leukemia (T-LGLL) using whole genome sequencing. To understand the molecular consequences of this mutation we introduced it into the mouse genome using CRISPR/Cas9 genome editing and deaminase base editing.

**Results** Using ChIP-seq and RNA-seq, we identified activity and formation of STAT5-dependent regulatory elements and expression of target genes that are altered by mutations. These findings provide insight into the initiation and progression of hematopoietic disease. Single cell RNA-seq and flow cytometry explored the impact of the STAT5B mutation on different immune cell populations and their genetic programs.

**Conclusions** Our study offers insights into pathogenic molecular immune mechanism elicited by STAT5 mutations. Our experimental approach provides a blueprint to investigate and understand mutations in autoimmune disease including lupus.