Plenary Session 1: Lupus in 2017: from molecular targets to new therapies

1 STEM CELLS AND THE TREATMENT OF SLE
L Sun. Nanjing, China
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Systemic lupus erythematosus (SLE) is a heterogeneous chronic multisystemic autoimmune inflammatory disorder. Autologous hematopoietic stem cell transplantation (HSCT) represents the first application of stem cell regenerative medicine in the treatment of drug-resistant SLE. The 5 year follow-up data showed that the overall survival was 84%, the probability of disease-free survival was 50% and treatment-related mortality was 4%. The European Group for Blood and Marrow Transplantation (EBMT) data showed that the 5 year overall survival was 81%±8% and disease-free survival was 29%±9%, with a non-relapse mortality of 15%±7%, suggesting a satisfactory clinical efficacy of autologous HSCT for lupus patients. However, The biggest challenge for HSCT is the high rate of disease relapse, as well as the serious side effects of the conditioning therapy. Mesenchymal stem cells (MSCs) are widely studied as an alternative cell source for their ability to differentiate into multiple mesenchymal lineages, as well as endoderm and neuroectoderm lineages. We have shown that bone marrow derived MSCs from SLE patients are defective structurally and functionally. Then from March 2007, we started to use allogeneic bone marrow and umbilical cord derived MSCs transplantation (MSCT) for refractory SLE patients, especially for those with drug resistant lupus nephritis. Allogenic MSCs were administered intravenously (one million cells per kilogram of bodyweight). The clinical manifestations and laboratory parameters were compared pre- and post-MSCT. During 4 years' follow up, complete remission was 28% at 1 year (23/83), 31% at 2 years (12/39), 42% at 3 years (5/12) and 50% at 4 years (3/6). Rates of relapse were 12% (10/83) at 1 year, 18% (7/39) at 2 years, 17% (2/12) at 3 years and 17% (1/6) at 4 years. Disease activity declined shown by significant changes in SLEDAI score, proteinuria, renal function, and levels of serum autoimmune antibodies, albumin and complement C3. Furthermore, we observed a long-term tissue repair effect by MSCs transplantation in our patients. Importantly, doses of corticosteroid and immunosuppressant were tapered or discontinued after MSCT. Taken together, allogeneic MSCT exerts a profound therapeutic effect in patients with severe and refractory SLE.

2 SHARED AND ENDOGAN SPECIFIC TRANSCRIPTIONAL NETWORKS IN SKIN VERSUS KIDNEY BIOPSY IN SYSTEMIC LUPUS
1CC Berthier*, 1J Stannard, 1EM Myers, 2R Namas, 1L Lowe, 1T Reed, 2A Davidson, 1M Kretzler, 1IM Kahnemberg. 1University of Michigan, Internal Medicine, Ann Arbor, USA; 2Feinstein Institute, Centre for Autoimmunity and Musculoskeletal Diseases, Manhasset- NY, USA
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Background and aims Skin rash can often herald the onset of a systemic disease flare in systemic lupus. The subtype of skin lesion may confer a differential risk of renal involvement. We hypothesised that renal flares may exhibit crosstalk between skin and kidneys and that similar molecular mechanisms may underlie skin and renal disease.

Methods We used systems biology approaches to integrate the regulatory events occurring in subacute cutaneous lupus erythematosus (sCLE, n=43) and discoid lupus erythematosus (DLE, n=47) and compared with those in the ERCB lupus nephritis (LN) class II+IV cohort (n=22).

Results Shared transcriptional networks in SLE skin lesions versus LN kidney biopsies reflect similar pathway regulation (p-value<0.05) including complement, B-cells, dendritic cells (DCs), IL4, IL8, and inflammasome signalling pathways.

IL-12 signalling and production in macrophages, IL-3, IL-15 signalling pathways were regulated only in LN glomeruli and sCLE rashes, while there were metabolic pathways unique to DLE.

CCL21 mRNA expression was specifically up-regulated in sCLE and LN tubulointerstitial and correlated with eGFR, which suggests it may play a role in cutaneous and renal lupus pathogenesis.

Conclusions SCLE, which is associated with a higher risk of systemic disease involvement compared with DLE, shares overlapping gene regulation with lupus nephritis. Dendritic cell pathways and associated upregulation of the CCR7 ligand CCL21, that is involved in recruitment of immune effector cells, may serve as a marker for sCLE patients at risk for LN. These data thus identify potentially important molecular targets for novel therapies in cutaneous and renal lupus.

3 CONFIRMATION OF 5 NOVEL SUSCEPTIBILITY LOCI FOR SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) AND INTEGRATED NETWORK ANALYSIS OF 82 SLE SUSCEPTIBILITY LOCI
1S Nath*, 1W Yang, 2Xi Zhou, 3C Sun, 4Y Okada, 5SC Bae, 6N Shen, 7J Molineros. 1Oklahoma Medical Research Foundation, Arthritis and Clinical Immunology, Oklahoma City, USA; 2The University of Hong Kong, Department of Paediatrics and Adolescent Medicine, Hong Kong, China; 3Peking University First Hospital- Peking University Institute of Nephrology, Renal Division, Beijing, China; 4Osaka University Graduate School of Medicine, Department of Statistical Genetics, Osaka, Japan; 5Hanyang University Hospital for Rheumatic Diseases, Department of Rheumatology, Seoul, Republic of Korea; 6Renji Hospital- Shanghai Institutes for Biological Sciences, Rheumatology, Shanghai, China
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Background and aims We recently identified ten novel SLE susceptibility loci in Asian populations and uncovered several additional suggestive loci requiring further validation. This study aimed to replicate five of these suggestive loci followed by meta-analysis, and perform a series of bioinformatic analyses on all 82 reported SLE loci to identify shared regulatory signatures.

Methods We investigated five loci in a Han Chinese cohort, and performed meta-analysis together with 11 656 cases and 23 968 controls from previously reported Asian and European populations. Epigenomic analysis was performed using ENCODE and GETEx data.

Results All five loci passed genome-wide significance: MYNN (rs10936599, Pmeta=1.92×10-13), ATG16L2 (rs11235604, Pmeta=8.87×10-12), CCL21 (rs223881, Pmeta=5.87×10-16), ANKS1A (rs2762340, Pmeta=4.93×10-15) and RNASEH2C (rs1308020, Pmeta=2.96×10-19) and co-located with annotated gene regulatory elements. The novel SLE loci share genetic signatures with other reported SLE loci, including
effects on gene expression, transcription factor binding, and epigenetic characteristics. Using the correlated SNPs (r² > 0.8) from the 82 SLE loci, we found only 1.5% SNPs encode missense or synonymous mutations, and the majority (56%) were implicated in differential expression of cis-genes (9.81 × 10⁻¹⁹ < P < 5 × 10⁻³). Significant over-representation (P < 0.05) of transcription factor binding sites for p53, MEF2A and E2F1. Enrichment analysis highlights the involvement of common pathways, gene ontology, protein domains, and the importance of these loci in B and T cell biology.

Conclusions We provide evidence of five novel SLE susceptibility loci. Integrated bioinformatic analysis using all 82 SLE loci revealed that SLE susceptibility loci share gene regulatory features, including significant enrichment of epigenetic marks and transcription factor binding sites, suggestive of shared regulatory mechanisms of SLE etiopathogenesis.

Plenary Session 2: Lupus nephritis: from bench to bedside

4 ACCELERATED LUPUS NEPHRITIS ASSOCIATED WITH INCREASED T HELPER SUBSET, SERUM TNFA AND ANTI DSDNA LEVELS IN PREGNANT PRISTANE INDUCED LUPUS MICE

1N Nurdiana*, 1U Kalum, 2E Sari Desti, 3K Handono, 4H Kalim. 1Brawijaya University, Clinical Pharmacology, Malang, Indonesia; 2Brawijaya University, Nursing, Malang, Indonesia; 3Brawijaya University, Clinical pathology, Malang, Indonesia; 4Brawijaya University, Rheumatology-Immunology Division-Internal Medicine, Malang, Indonesia

Background and aims To investigate the role of T helper (Th) cell subsets and TNFα in the pathogenesis of nephritis in pregnant SLE mice model.

Methods Thirty female Balb/c mice were divided into two groups: non-pregnant and pregnant lupus mice. SLE induction was done by single intraperitoneal injection of 0.5 cc pristane. After twelve weeks post injection, mice were mated. Periodically, blood pressure was monitored and urine albumin was measured by ELISA. After 18 days, mice were euthanized, and renal biopsy was done to evaluate the development of nephritis. Placental TNFα and serum anti-dsDNA were measured by ELISA. Spleen Th1, Th2, and Th17 percentages were measured by flowcytometry.

Results Th1, Th2, and Th17 percentages in were significantly higher in pregnant lupus mice compared to non pregnant group. Th1 and Th17 percentages were positively correlated with albuminuria, anti-dsDNA, systolic, and diastolic blood pressure. Incidence of lupus nephritis was higher in pregnant lupus mice with higher activity index compared to non pregnant mice. The activity index also had positive correlations with higher placental TNFα and anti-dsDNA levels in pregnant lupus mice. Placental TNFα and anti-dsDNA levels were positively correlated with albuminuria. Moreover, placental TNFα levels were positively correlated with systolic and diastolic blood pressure.

Conclusions High percentages of Th cell subsets, TNFα and anti-dsDNA antibody were associated with renal disorder in pregnant lupus mice which propose a new mechanism for the pregnancy complication in SLE.

5 IMPACT OF VASCULAR INVOLVEMENT ON OUTCOMES IN PATIENTS WITH LUPUS NEPHRITIS

1M Rathi*, 2H Prasad, 3A Sharma, 4R Nada, 5YJ Gupta. 1Postgraduate Institute of Medical Education and Research, Nephrology, Chandigarh, India; 2Postgraduate Institute of Medical Education and Research, Internal Medicine, Chandigarh, India; 3Postgraduate Institute of Medical Education and Research, Histopathology, Chandigarh, India

Background and aims The exact incidence and significance of vascular involvement (VI) in patients of lupus nephritis (LN) is not clear.

Methods All renal biopsy confirmed LN cases over a five years were included. The biopsy was reviewed and subjects were divided into two subgroups: Group 1 (VI present), and Group 2 (VI absent). Morphological lesions of lupus vasculopathy, vascular thrombotic microangiopathy (TMA), vasculitis, vascular immune deposits and arteriosclerosis were taken as VI. Clinical details and treatment received were noted and the outcomes were assessed at the end of six months.

Results A total of 241 biopsy proven LN patients (211 females, 30 males) with mean age of 29.79±9.44 years were included. The VI was seen in 78 patients (32.3%, Group 1). Vascular immune deposits was seen in 13 (5.3%), lupus vasculopathy in 5 (2.0%), vasculitis in 2 (0.8%), vascular TMA in 27 (11.2%) and arteriosclerosis in 55 (22.8%) patients. There was no difference between the two groups at baseline, except for a higher serum creatinine in Group 1 (1.87 vs 1.43 mg/dL, p=0.004). At the end of six months of treatment, Group 1 patients had higher 24 hour protein excretion (11.0±6.14 vs 8.88±2.23 gms/day, p=0.001) and higher serum creatinine (1.35±1.25 vs 0.92±0.56 mg/dL, p=0.001). 38.2% patients in Group 1 achieved complete remission as compared to 61.9% in Group 2 (p=0.006), while, 26.3% patients in Group 1 had resistant disease as compared to 14.3% in Group 2 (p=0.02).

Conclusions LN patients with VI have more severe renal presentation and poorer outcomes.

Plenary Session 3: Challenges in drug development and clinical trial design in SLE

6 THE IDEAL TRIAL DESIGN: A FOCUS ON PATIENT SELECTION AND APPROPRIATE OUTCOME MEASURES

R Furie*. USA

Although the lupus community has not witnessed the same growth in drug approvals as in inflammatory arthritis, there have been major breakthroughs since the mid-twentieth century. The discovery in the late 1940's of cortisone revolutionised the treatment of patients not only with lupus but with all inflammatory diseases. During the 1950's, azathioprine was introduced as a chemotherapeutic agent, but it was adopted soon thereafter as a drug for patients with rheumatic diseases. The antimalarial quinacrine was first used in the early 1950's as well. The application of cyclophosphamide, the eighth cytotoxic anticancer drug approved by the FDA, to patients with