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

1 STEM CELLS AND THE TREATMENT OF SLE

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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 (MSCST) 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 tampered or discontinued after MSCT. Taken together, allogeneic MSCST exerts a profound therapeutic effect in patients with severe and refractory SLE.

2 SHARED AND ENDORGAN SPECIFIC TRANSCRIPTIONAL NETWORKS IN SKIN VERSUS KIDNEY BIOPSIES IN SYSTEMIC LUPUS

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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 tubulointerstitium 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

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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), CCL22 (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
ACCELERATED LUPUS NEPHRITIS ASSOCIATED WITH IMPACT OF VASCULAR INVOLVEMENT ON OUTCOMES: THE IDEAL TRIAL DESIGN: A FOCUS ON PATIENT SELECTION AND APPROPRIATE OUTCOME MEASURES

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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 were 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 (1.10±1.64 vs 0.88±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.

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

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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 level was measured by ELISA. After 18 day, 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 Th1 and Th2 percentages. Higher placental TNFα and anti-dsDNA levels were found 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, TNF α and anti ds DNA antibody were associated with renal disorder in pregnant lupus mice which propose a new mechanism for the pregnancy complication in SLE.