CONTACT DYNAMICS BETWEEN MESENCHYMAL STEM CELLS AND T CELLS IN LUPUS-PRONE MRL/lpr MOUSE MODEL

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Background Systemic lupus erythematosus (SLE) is a multi-organ autoimmune disease characterized by autoimmune production and mesenchymal stem cells (MSCs) have emerged as a promising new therapy for the treatment of SLE. MSCs are adult stem cells isolated from various human tissues including bone marrow, adipose tissue, umbilical cord blood, and skeletal muscle; MSCs can differentiate into various cell types and can potentially replace damaged cells in vivo. MSCs suppress T cell proliferation and cytokine production, reduce B cell proliferation and antibody secretion, decrease the generation and function of dendritic cells, and reduce the activity of natural killer cells. MSCs also enhance the activity of regulatory T (Treg) cells. MSCs are thought to inhibit T cell functions by two different mechanisms: by producing soluble mediators and by direct cell-cell contacts. The soluble immunosuppressive factors produced by MSCs include IL-10, nitric oxide (NO), tumor growth factor (TGF)-β, prostaglandin E2 (PGE2), and indoleamine 2,3-dioxygenase (IDO), all of which can inhibit the functions of major immune cells. Yet, much remains to be learned about the contact-dependent T cell inhibition by MSCs.

Methods We examined the in vitro efficacy of MSCs in lupus-prone MRL/lpr mouse model and examined how MSCs inhibit MRL/lpr T cells by using time-lapse imaging at the single level.

Results In this study, we show that transfer of human MSCs increased MRL/lpr mouse survival, decreased T cell infiltration in the kidneys, and reduced T cell cytokine expression. In vitro, allogeneic mouse MSCs inhibited MRL/lpr T cell proliferation and cytokine production. Time-lapse imaging revealed that MSCs recruited MRL/lpr T cells establishing long-lasting cellular contacts by enhancing T cell VCAM-1 expression in a CCL2-dependent manner. In contrast, CCL2 deficient MSCs did not induce T cell migration and VCAM-1 expression, resulting in insufficient cell-cell contact. Consequently, CCL2 deficient MSCs did not inhibit IFN-γ production by T cells and upon transfer no longer prolonged survival of MRL/lpr mice.

Conclusions Taken together, our imaging study demonstrates that CCL2 enables the prolonged MSC-T cell interactions needed for sufficient suppression of autoreactive T cells and helps to understand how MSCs ameliorate symptoms in lupus-prone MRL/lpr mice.

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Methods The Medical Outcomes Study Short Form (SF-36) and the Lupus Quality of life (LupusQol) were applied in a cohort of 38 SLE patients. At the time of HRQOL testing, all patients underwent a clinical and laboratory evaluation, together with the measure of disease activity using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K). In addition, a battery of psychological tests including the Hamilton Anxiety Scale (HAS) and the Hamilton Depression Rating Scale (HAM-D) was applied.

Results The parameters which seemed to greatly influence the impairment of HRQOL were female gender, marital statues, a higher SLEDAI-2k scores as well as higher HAS and HAM-D scores. Arthralgia-arthritis, cutaneous disease activity, neurological disease activity and renal disease activity were correlated negatively with LupusQol subscales. There was a strong positive correlation between comparable domains of instruments. Although not as strong as comparable domains, significant correlations were also found between noncomparable domains of LupusQol and PCS and MCS of SF-36.

Conclusions SF-36 and LupusQol were both beneficial instruments in evaluating HRQOL of Tunisian patients with SLE. Anxiety, depression and disease activity in some organs seem to be the major determinants of HRQOL impairment in SLE patients.

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54 BLOOD CONCENTRATIONS OF COMPLEMENT SPLIT PRODUCT IC3B AND SERUM C3 ASSOCIATE WITH SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY

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Background A major unmet need in SLE is the identification of a biomarker that consistently tracks with disease activity. One current approach is measuring complement activation by evaluating consumption of serum C3 and C4. However, since they are acute phase reactants, interpretation of these levels is challenging as serum levels may not decrease until late in a disease flare. iC3b is a proteolytically derived molecule of C3b and increases with complement activation. iC3b/C3 ratio measures complement consumption relative to production, which may provide for a more accurate assessment of complement activation. We hypothesize that blood iC3b and iC3b/C3 levels will provide a more specific and reliable marker of complement activation and disease activity in SLE.

Methods 159 consecutive subjects with American College of Rheumatology or Systemic Lupus International Collaborating Clinics classified SLE were enrolled into CASTLE (Complement Activation Signatures in Systemic Lupus Erythematosus), a prospective observational study. Patients with 1–7 study visits were included in this longitudinal analysis. 48 healthy volunteers were enrolled to establish the normal reference iC3b/C3 ratio. Serum C3 and C4 were measured by nephelometry and blood iC3b levels by a lateral flow assay. SLE disease activity was monitored utilizing the Systemic Lupus Erythematosus Disease Activity Index 2K Responder Index-50 instrument.

Results iC3b/C3 ratio, double-stranded (ds)DNA antibodies (Abs), and supraphysiologic prednisone dose (>7.5 mg/day) each independently correlated with SLE disease activity, employing multilevel multiple logistic regression analysis. Only the iC3b/C3 ratio was significantly associated with clinically meaningful improvements in disease activity among subjects receiving supraphysiologic doses of prednisone. iC3b/C3 outperformed C3 and C4 levels discriminating both active versus inactive SLE disease and major flares versus no disease activity. iC3/C3, dsDNA Abs, ESR, and supraphysiologic prednisone dose were independently associated with lupus nephritis, while none were associated with SLE rash. The association of iC3b/C3 with nephritis was independent of other observed clinical manifestations. Finally, we observed a stronger association of the iC3b/C3 ratio with SLE disease activity in African-Americans compared to Whites.

Conclusions Blood iC3b/C3 correlates with SLE disease activity and clinically meaningful changes. Furthermore, it discriminates between active versus inactive SLE, and major flares compared to those patients without active disease. Differences in the strength of association was observed between races and manifestations.

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55 POOR SLEEP QUALITY ASSESSED SUBJECTIVELY ASSOCIATED WITH WORSENING SLE DISEASE ACTIVITY

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Background Poor sleep quality is commonly observed in patients with SLE. We hypothesize that poor sleep contributes to worsening SLE. The aims of this study are to evaluate the relationship between subjective sleep measures and SLE activity over time.

Methods A prospective, observational study evaluated the relationship between sleep and SLE disease activity. 151 patients were enrolled. Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Patient Reported Outcomes Measurement Instrument System (PROMIS)-Sleep Related Impairment (SRI), and PROMIS-Sleep Disturbance (SD) survey instruments measured patient reported sleep quality. The population mean for the PROMIS instruments is 50. The SLEDAI-2000 Responder Index-50 (S2K RI-50) was used to define active SLE as S2K RI-50 >4 and worsening SLE at subsequent visits as an increase in S2K RI-50 ≥4. Baseline comparisons were calculated using non-parametric tests. Kaplan-Meier examined the relationship between poor sleep and worsening SLE activity over time.

Results At baseline, the median age was 42, 90.7% were female, 54.3% were African American, 24.5% were on prednisone doses >7.5 mg/day, and 36.4% had active SLE. Patients with active SLE had significantly higher SRI scores (median 64.3) vs inactive SLE (median 56.6) as well as significantly higher SD scores (median 58.3 vs 52.2), whereas PSQI and ESS were not significantly different.

Data from 109 patients with ≥2 visits were used for longitudinal studies. Kaplan-Meier analysis, stratified by SRI T-score of >60 vs ≤60 demonstrated that worse sleep (SRI >60) at the...