POS0761

INVESTIGATION ON THE EFFECT AND MECHANISM OF ABNORMALLY ACTIVATED CD8+ T CELLS FROM BONE MARROW ON HEMATOPOIETIC STEM CELLS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

T. Fu¹, Y. Yang¹, X. Gu², C. Dong², R. Zhao¹, J. Ji², Z. Xue¹, X. Zhang³, Z. Gu².
¹Affiliated Hospital of Nantong University, Research Center of Clinical Medicine, Nantong, China; ²Affiliated Hospital of Nantong University, Department of Rheumatology, Nantong, China; ³Institute Pasteur of Shanghai Chinese Academy of Sciences, Key Laboratory of Molecular Virology & Immunology, Shanghai, China

Background: SLE is an autoimmune disease characterized by the abnormal function of lymphocytes. The impairment of hematopoietic function of bone marrow participates in its pathogenesis, in which T cells play an important role. However, study on bone marrow T cells in SLE patients is very limited.

Objectives: This study aims to characterize the phenotype and molecular characteristics of abnormally activated CD8+T cells in bone marrow of SLE patients and explore the mechanism of hematopoietic stem cells (HSCs) reduction caused by the abnormally activated CD8+T cells in bone marrow of patients with SLE.

Methods: A total of 8 SLE patients and 5 age- and sex-matched controls were recruited in our study. Among them, 3 SLE patients and 4 donors were collected bone marrow and peripheral blood samples for Single-cell RNA sequencing (scRNA-seq) and functional studies. BM and peripheral T cell subsets were measured by flow cytometry. Plasma cytokines and secreted immunoglobulins were detected by Luminex. Disease activity of SLE patients was measured using the SLE Disease Activity Index (SLEDAI). All analyses were performed using R language and Flowjo 9.

Results: In the present study, SLE patients had increased CD8+T% $\alpha\beta$ T cells and decreased CD4+T% $\alpha\beta$ T cells in bone marrow of SLE, compared to healthy controls. A large number of CD38+HLADR+CD8+T cells existed in the bone marrow and peripheral blood of SLE patients. Those patients also showed reduced number of HSCs, and with a downward trend of the numbers of peripheral red blood cells, white blood cells, neutrophils, hemoglobin, and platelets. By scRNA-seq, the CD38+HLADR+CD8+T cells contained high levels of GZMK, GZMA, PRF1, IFNG, and TNF in the bone marrow of SLE patients. the CD38+HLADR+CD8+T cells exhibited significant relationship with HSCs, white blood cells, neutrophils, and platelets.

Conclusion: These findings demonstrated that the abnormally activated CD8+T cells in bone marrow can reduce the number of HSCs by the expression of killer molecules, which contributes to the impairment of hematopoietic function and the development of SLE. This project focuses on the specific bone marrow T cell subset in SLE. The complementation of this project provides information for exploring the mechanism of hematopoiesis involvement.

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CAN THE SLE-DAS SUBSTITUTE BILAG TO MEASURE LUPUS DISEASE ACTIVITY IN CLINICAL TRIALS? POST-HOC ANALYSIS OF THE BLISS-76 TRIAL

D. Jesus^{1,2}, A. Matos^{3,4}, C. Henriques^{3,5}, A. Doria⁶, L. Inês^{2,7}. ¹Centro Hospitalar de Leiria, Rheumatology Department, Leiria, Portugal; ²University of Beira Interior, Faculty of Health Sciences, Covilhã, Portugal; ³Institute of Viseu, Technology and Management, Viseu, Portugal; ⁴Research Centre in Digital Services, CISEd, Viseu, Portugal; ⁵University of Coimbra, Centre for Mathematics, Coimbra, Portugal; ⁶University of Padova, Division of Rheumatology, Padova, Italy; ⁷Centro Hospitalar e Universitário de Coimbra, CHUC Lupus Clinic, Rheumatology Department, Coimbra, Portugal

Background: The primary endpoint for randomized clinical trials (RCT) in Systemic lupus erythematosus (SLE) is usually defined as proportion of responders in a composite index. The most widely used are British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) and Systemic Lupus Responder Index (SRI). Both comprise BILAG along with SLE Disease Activity Index (SLEDAI). BICLA and SRI are complex and time-consuming to assess. The SLE Disease Activity Score (SLE-DAS) is an easy to apply, validated, continuous disease activity measure, highly correlated with SLEDAI, with higher accuracy and sensitivity to change as compared to SLEDAI¹.

We hypothesize that SLE-DAS can also identify the SLE disease activity information from BILAG, thus dispensing the use of composite indexes for RCT.

Objectives: To compare the ability of the SLE-DAS and the Safety of Estrogen in Lupus National Assessment (SELENA)-SLEDAI to discriminate between BILAG classification of mild vs. moderate vs. severe disease activity.

Methods: Post-hoc analysis of all intention-to-treat patients in the BLISS-76 (NCT00410384) RCT at the baseline study visit. SELENA-SLEDAI and BILAG were assessed at time of the study visits and SLE-DAS was retrospectively scored from the study database. Patients' disease activity was classified as: (i) mild (no BILAG B or A scores in any organ domain); (ii) moderate (1 BILAG B, no A scores); (iii) severe (≥ 2 BILAG B and/or ≥ 1 BILAG A). Ability of the SLE-DAS and SELENA-SLEDAI to differentiate between: (i) mild vs. moderate/severe disease activity; (ii) mild/moderate vs. severe disease activity (according to BILAG), were evaluated using receiver operating characteristic (ROC) analysis. The area under the ROC curves (AUCs) with 95% confidence intervals (95%CI) as a measure of discriminatory ability of the SLE-DAS and SELENA-SLEDAI were compared using Delong's test for two correlated curves. Because AUC measurements might have restricted accuracy for imbalanced datasets, precision-recall (PR) curves and area under PR curves (AUC-PR) were also performed. Statistical significance was set at 0.05.

Results: We included 819 patients, classified by BILAG as presenting mild (7.7%), moderate (28.8%) or severe (63.5%) disease activity. To differentiate mild vs. moderate/severe disease activity, the discriminatory ability of SLE-DAS was outstanding (AUC 0.948; 95%CI 0.923-0.973), while that of SELENA-SLEDAI was acceptable (AUC 0.729; 95%CI 0.657-0.801) ($p < 0.005$) (figure 1A). To differentiate mild/moderate vs. severe disease activity, the discriminatory ability of SLE-DAS was excellent (AUC 0.873; 95%CI 0.846-0.899), while that of SELENA-SLEDAI was acceptable (AUC 0.707; 95%CI 0.670-0.744) ($p < 0.005$) (figure 1B). The AUC-PR confirmed the higher performance of SLE-DAS over SELENA-SLEDAI to differentiate mild vs. moderate/severe disease activity (0.995 vs. 0.965, respectively) (figure 1C) and mild/moderate vs. severe disease activity (0.902 vs. 0.794, respectively) (figure 1D).

Figure 1. Receiver operating characteristics (ROC) curves comparing the ability of the SLE-DAS and SELENA-SLEDAI to differentiate (A) mild vs. moderate/severe disease activity and (B) mild/moderate vs. severe disease activity, as assessed by BILAG; and Precision-recall (PR) curves comparing the performance of the SLE-DAS and SELENA-SLEDAI to differentiate (C) mild vs. moderate/severe disease activity and (D) mild/moderate vs. severe disease activity.

Conclusion: The SLE-DAS presents excellent performance in assessing SLE disease activity categorized by BILAG scores, which is not the case for SELENA-SLEDAI. Further studies will aim to better define ability of SLE-DAS to substitute composite responder indices.

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