AB0173

LONG NON-CODING RNA, LINC00487 EXPRESSION IS UPREGULATED IN B CELLS AND CORRELATES TO DISEASE ACTIVITY IN PATIENTS WITH PRIMARY SJÖGREN'S SYNDROME

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Background: Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterized by interferon signature [1] and exocrine gland dysfunction which leads to dryness of the eyes and mouth [2]. B cells are considered to play an important role in the pathogenesis of pSS. Dysregulation of B cells can lead to production of anti-Sjögren's syndrome-related antigen A (anti-SSA) autoantibodies.

Objectives: We investigated the differential gene expression of peripheral B cell subsets to reveal the precise role of B cells in the pathogenesis of pSS.

Methods: We enrolled pSS patients (n=6) and healthy controls (HC) (n=6), with matching for age and sex. Peripheral B cells acquired from the participants were separated by cell sorting into 4 subsets: CD38⁺IgD⁺, CD38⁺IgD⁺, CD38^{high}IgD⁺ and CD38⁺IgD⁻. Total RNA was extracted and gene expression was measured using the Human Genome U133 Plus 2.0 Array (Affymetrix). The data were bioinformatically analyzed with reference to the corresponding clinical information.

Results: Using principal component and clustering analyses, we found that transcript expression patterns depended on cell type rather than clinical condition (pSS or HC). Interferon signaling was the most upregulated pathway in many of B cell subsets of pSS patients. As well as HLA and interferon signature genes, LINC00487 was upregulated significantly in all B cell subsets. Its fold changes in CD38⁺IgD⁺, CD38⁺IgD⁺, CD38^{high}IgD⁺ and CD38⁺IgD⁻ were 8.4 (p=0.038), 11.3 (p=0.014), 8.5 (p=0.089) and 6.37 (p=0.078), respectively. In addition, the normalized intensity value of LINC00487 was significantly correlated with disease activity score in all pSS B cell subsets, namely CD38⁺IgD⁺ (Figure A, r=0.96, p=0.002), CD38⁺IgD⁺ (Figure B, r=0.90, p=0.015), CD38^{high}IgD⁺ (Figure C, r=0.81, p=0.049) and CD38⁺IgD⁻ (Figure D, r=0.96, p=0.003). The expression of LINC00487 in B cell lines was regulated by IFN α .

Conclusion: Compared to HC, patients with pSS showed upregulation of the interferon signaling pathway and LINC00487 gene in all B cell subsets. This upregulation correlated with disease activity and regulated by IFN α in B cell lines. These results may suggest that long non-coding RNA contributes to B cell dysregulation in patients with pSS and the precise role of LINC00487 in B cell and pathogenesis of pSS requires further study.

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Figure. Correlation between the expression of LINC00487 and disease activity score in each B cell subset.

ESSDAI; EULAR Sjögren's Syndrome Disease Activity Index

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AB0174

CLINICAL SIGNIFICANCE OF THE URINARY CD11C+ MYELOID CELLS IN THE PATIENTS WITH LUPUS NEPHRITIS

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Background: It is known that various immune cell populations play important pathogenic roles in lupus nephritis (LN). Kidney-infiltrating myeloid cells are responsible for the pathology in murine model for LN. However, the characteristics of myeloid cells in patients with LN have not previously been investigated because of difficulties of access to affected tissue. Recent studies have reported that the urine has become an alternative substitute for kidney tissue to study renal pathology.

Objectives: Therefore, we investigated the characteristics and functions of urinary myeloid cells in patients with LN.

Methods: Within viable CD45+ cells, the frequency and absolute numbers of myeloid cells in the urine were examined after exclusion of lymphoid cells by expression of CD3, CD19 and CD56. Expression of phenotypic markers and

production of pro-inflammatory cytokines were analyzed in urinary myeloid cells of patients with LN.

Results: Myeloid cells were identified by the expression of CD45+ and CD11c+ in the urine of patients with LN. The frequency and absolute numbers of myeloid cells were markedly increased in the urine of patients with proliferative LN than non-proliferative LN. In addition, titers of anti-dsDNA antibodies were correlated with the frequency or numbers of urinary CD11c+ myeloid cells. These urinary CD11c+ myeloid cells showed the phenotypes of infiltrated monocyte-derived cells rather than tissue-resident macrophage. In addition, CD11c+ myeloid cells were localized in tubulointerstitium and had capacity to produce pro-inflammatory cytokines including IL-6. Further, we found that there was a significant population of tubule cells in the urine, which is correlated with the frequency of CD11c+ myeloid cells.

Conclusion: Our results indicate that CD11c+ myeloid cells are present in the urine and contribute to tubulointerstitial inflammation in proliferative LN.

Disclosure of Interests: None declared

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AB0175 ABSOLUTE REDUCTION OF PERIPHERAL CD4+CD25+FOXP3+T REGULATORY CELLS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: T lymphocytes are important contributors to systematic lupus erythematosus (SLE). Regulatory T (Treg) cells, with the capacity to suppress immune responses, effector T cells (Teff), which promote inflammation, have been intensively studied in recent years. However, previous reports describing the respective changes of Treg and Teff, especially T helper cells (Th17) in SLE patients were controversial. Here, we investigated both absolute number and percentage of CD4+CD25+Foxp3+Treg (CD4Treg) cells and effector cells on a large scale and the role of low-dose interleukin-2 (IL-2) in SLE.

Objectives: To investigate both absolute number and percentage of CD4+CD25+Foxp3+Treg (CD4Treg) cells and effector cells on a large scale and the role of low-dose interleukin-2 (IL-2) in SLE.

Methods: Two hundred and thirty-five SLE patients (219 women and 16 men), with mean age of 37.80 ± 14.00 years, were enrolled. The absolute count and percentage of subpopulation of peripheral blood (PB) lymphocyte in these patients were measured by flow cytometry combined with internal microsphere standard. And low-dose IL-2 was used among 127 patients at a dosage of fifty WIU every day for five days. Immunological and clinical assessments were performed again at the end of IL-2 treatment. Ninety healthy volunteers, matched for patients' age and gender, were also included for the estimation of lymphocyte subsets.

Results: As compared to healthy controls (median of Treg cells: 33.09 cells/ul), the absolute number of circulating CD4Treg cells were significantly decreased in SLE patients (median: 15.49 cells/ul, $P < 0.001$). The median ratios of Th17/Treg cells in patients were greatly higher than those of healthy volunteers [0.42 (0.19, 0.88) vs. 0.21 (0.15, 0.34), $P < 0.001$], while there was not significantly different in peripheral Th17 cell between two groups. Besides, Th1, Th2, CD8+T, B cells and their respective ratios to Treg cells were like that of Th17 cells as well. Moreover, CD4Treg cells were negatively correlated with ESR and SLEDAI score ($r = -0.198$, $P = 0.01$; $r = -0.25$, $P = 0.002$). While no obvious correlation was seen between Th17 cells and SLEDAI score. After IL-2 therapy in SLE, there was a four-fold increase in circulating CD4Treg cells [43.73 (24.08, 74.22) vs. 11.95 (7.51, 20.34), $P < 0.001$], whereas Th17 cells were increased slightly. The ratio of Th17/Tregs was decreased significantly in patients with IL-2 treatment [0.19 (0.09, 0.41) vs. 0.52 (0.23, 0.95), $P < 0.001$], tended to balance and had no difference with healthy individual ($P = 0.275$). Similarly, there were same trends in Th1, Th2, CD8+T, B and NK cells.

Conclusion: The reduction of CD4Tregs but not the elevation of effector cells may be the major reason for imbalance of Teff/Treg, indicating that SLE is an autoimmune disease triggered by the defect of immunotolerance. More importantly, low-dose IL-2 might promote the proliferation of various lymphocyte subpopulation, and mainly modulated the abundance and immunosuppression activity of Tregs, which effectively induced autoimmune tolerance and further improved clinical symptoms.

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AB0176 MITOGEN- AND STRESS-ACTIVATED PROTEIN KINASE-1 (MSK1) AS THE LINK BETWEEN MIR-130A-DYSREGULATION AND CDC2-ACTIVATION IN SJÖGREN'S SYNDROME

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Background: Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterized by lymphocytic infiltration of the exocrine glands and dryness of mouth and eyes. T and B lymphocytes that infiltrate the salivary glands play a central role in local production of autoantibodies and cytokines, associated with dryness and tissue-damage. Type-2 conventional dendritic cells (cDC2) are very potent antigen-presenting cells and have the ability to produce a variety of cytokines involved in T and B cell activation, germinal centres formation and autoantibody production.

Objectives: Considering the critical role of microRNAs (miRNAs) in regulation of cell activation, we investigated their potential dysregulation in circulating cDC2s of patients with pSS compared to healthy controls (HC).

Methods: CD1c-expressing cDC2s were isolated from peripheral blood of pSS patients and controls from two independent cohorts. In the donors from the discovery cohort (15 pSS, 6 HC) the expression of 758 miRNAs was screened; the replication cohort (14 pSS, 11 HC) was used to confirm consistent differential expression of 18 identified miRNAs. A quantitative mass spectrometry-based technique (pSILAC) in HEK-293T cells was used to identify novel targets of the replicated miRNAs. Target-miRNA interaction was replicated in primary cDC2s. Differences in cytokine production between pSS and HC cDC2s were evaluated by FACS. cDC2s were cultured in the presence of different MSK1-inhibitors to examine their effect on cytokine production.

Results: The expression of miR-130a and miR-708 was consistently decreased in cDC2s from pSS patients compared to HC in both cohorts, and both miRNAs were downregulated upon stimulation via TLR3 and TLR7/8. MSK1 was identified as a novel target of miR-130a and overexpression of miR-130a reduced MSK1 protein expression in both HEK-293T cells and primary cDC2s. In-line with the regulation of MSK1 by miR-130a, MSK1 expression was higher in cDC2s of pSS patients as compared to controls. An increased frequency of cDC2s producing IL-12 and TNF- α was observed in pSS patients compared to HC, consistent with the central role of MSK1 in regulation of cytokine production. Exposure to either of two different MSK1 inhibitors in vitro reduced cDC2 activation and the production of IL-12, TNF- α and IL-6.

Conclusion: We here provide the first evidence of molecular dysregulation of cDC2s in pSS, including decreased expression of miR-708 and miR-130a, which can result from TLR activation, and enhanced production of pro-inflammatory cytokines. In view of its central role in NF- κ B signalling, inhibition of MSK1 to decrease cell activation and inhibit pro-inflammatory cytokine production represents a novel therapeutic avenue for treatment of Sjögren's Syndrome.

Disclosure of Interests: None declared

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AB0177 ARE THERE ANY CLINICAL AND SEROLOGICAL DIFFERENCES BETWEEN PATIENTS WITH PRIMARY AND SECONDARY (SLE) ANTIPHOSPHOLIPID SYNDROME?

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Background: Antiphospholipid syndrome (APS) could be diagnosed as primary (PAPS) or secondary (SAPS - accompanying other diseases, mainly found in patients with systemic lupus erythematosus -SLE)

Objectives: The aim of our study was to determine if pts with PAPS and SAPS had different clinical and serological status.