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THU0231

IL-2 DRIVES THE CONVERSION OF T FOLLICULAR HELPER TO T FOLLICULAR REGULATORY CELLS THROUGH EPIGENETIC MODIFICATION IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Systemic lupus erythematosus (SLE) is a complex polygenic autoimmune disease characterized by immune-system aberrations. Among several types of immune cells, T follicular helper (T_{fh}) cells promote autoantibody production, whereas T follicular regulatory (T_{fr}) cells suppress T_{fh}-mediated antibody responses.⁽¹⁾

Objectives: To identify the characteristics of T_{fr} cells and to elucidate the mechanisms of conversion of T_{fh} cells to T_{fr} cells, we probed the phenotype of T helper cells in patients with SLE and underlying epigenetic modifications by cytokine-induced signal transducer and activators of transcription (STAT) family factors.

Methods: Peripheral blood mononuclear cells from SLE patients (n=44) and healthy donors (HD; n=26) were analyzed by flow cytometry. Memory T_{fh} cells were sorted and cultured under stimulation with T cell receptor and various cytokines. Expression of characteristic markers and phosphorylation of STATs (p-STATs) were analyzed by flow cytometry and quantitation PCR. Histone modifications were evaluated by chromatin immunoprecipitation.

Results: The proportion of CXCR5⁺FoxP3⁺ T_{fr} cells in CD4⁺ T cells tended to increase (2.1% vs 1.7%, p=0.17); however, that of CD4⁺CD45RA⁺FoxP3^{hi} activated T_{fr} cells in T_{fr} cells was decreased (4.8% vs 7.1%, p<0.05), while CD4⁺CD45RA⁺FoxP3^{low} non-suppressive T_{fr} cells was increased (50.1% vs 38.2%, p<0.01) in SLE compared to HD. The percentage of PD-1^{hi} activated T_{fh} cells was significantly higher in SLE compared to HD (15.7% vs 5.9%, p<0.01). Furthermore, active patients had a higher ratio of activated T_{fh}/T_{fr} cells compared to inactive patients. In vitro study showed that IL-2, but not other cytokines such as TGF-β1, IL-12, IL-27, and IL-35, induced the conversion of memory T_{fh} cells to functional T_{fr} cells characterized by CXCR5⁺Bcl6⁺Foxp3^{hi}pSTAT3⁺pSTAT5⁺ cells. The loci of *FOXP3* at STAT binding sites were marked by bivalent histone modifications. After IL-2 stimulation, STAT5 directly bound on *FOXP3* gene loci accompanied by suppressing H3K27me3. Finally, we found that serum level of IL-2 was decreased in SLE and that stimulation with IL-2 suppressed the generation of CD38⁺CD27⁺B cells by ex vivo coculture assay using T_{fh} cells and B cells isolated from human blood.

Conclusion: Our findings indicated that the regulatory function of T_{fr} cells is impaired due to the low ability of IL-2 production and that IL-2 restores the function of T_{fr} cells through conversion of T_{fh} cells to T_{fr} cells in SLE. Thus, the reinstatement of the balance between T_{fh} and T_{fr} cells will provide important therapeutic approaches for SLE.

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THU0232

INTERFERON SIGNATURE IN LUPUS KIDNEY IS CORRELATED WITH REMISSION WITHIN 56 WEEKS

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Background: Activation of the type I interferon (IFN) pathway has been implicated in the initiation of systemic lupus erythematosus (SLE) and most SLE patients show increased expression of IFN-regulated genes in peripheral blood mononuclear cells or whole blood. However, the IFN signature in lupus kidney is not well examined especially at single cell resolution.

Objectives: To clarify the significance of the IFN signature in lupus kidney at single cell resolution

Methods: 18 lupus kidney (LN) and 34 transplanted kidney (KTx) samples were included in the study. Residual frozen kidney biopsies were collected after clinical diagnosis. The tissue from one donor was split into two. One portion was used for total RNA-Seq (tRNA-Seq) by SMARTer Stranded Total RNA-Seq Kit v2 - Pico Input Mammalian (Takara/Clontech). The rest was used for single nucleus RNA-Seq (snRNA-Seq) using Chromium Single Cell 3' Reagent Kits v3 (10x Genomics) (7 LN and 17 KTx). For the tRNA-Seq, the sequence reads were aligned to Ensembl genome annotation (Ens93) by STAR and the aligned reads were counted by htseq. IFN score of tRNA-Seq was calculated using the reported method [1] per each module (M1.2, M3.4 and M5.12). For the snRNA-Seq, the sequenced reads were processed on the standard pipeline of Cell Ranger (10x Genomics) and the data was visualized using Seurat. IFN score of snRNA-Seq was computed by the method reported by Arazi A, et al [2].

Clinical outcomes of LN were examined on the medical records retrospectively and the clinical remission in 56 weeks for LN was defined as a urinary protein/creatinine ratio less than 0.5 g/gCr.

Results: 11 LN had clinical remission and 7 LN showed non remitted disease within 56 weeks after the biopsy. There were no statistical significance co-variants such as age, gender and WHO class in pathology. IFN score of M1.2, M3.4 and M5.12 were significantly increased in LN with remission within 56 weeks (median 0.773 vs 0.659, 0.595 vs 0.243 and 0.415 vs 0.100: p-value 0.03, 0.01 and 0.02 [Wilcoxon rank-test]) in tRNA-Seq. In the snRNA-Seq, the lupus kidney with low IFN score showed restricted IFN signature in the endothelial cells mainly, which can be detected even in the controls, but those with high IFN score indicated broadly spread IFN signature among all of the cell types.

Conclusion: LN with high IFN score in kidney tissue is correlated with remission within 56 weeks. LN with low IFN score showed IFN signature restricted to endothelial cells but those with a higher IFN score revealed broadly affected cell types with IFN signature. These results suggest that the IFN signature of LN may start from endothelial cells and then spread to the whole kidney.

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