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Ⅲ. 研究成果の刊行物・別刷

Nucleosome-Specific Regulatory T Cells Engineered by Triple Gene Transfer Suppress a Systemic Autoimmune Disease[1]

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The mechanisms of systemic autoimmune disease are poorly understood and available therapies often lead to immunosuppressive conditions. We describe here a new model of autoantigen-specific immunotherapy based on the sites of autoantigen presentation in systemic autoimmune disease. Nucleosomes are one of the well-characterized autoantigens. We found relative splenic localization of the stimulative capacity for nucleosome-specific T cells in (NZB × NZW)F_1 (NZB/W F_1) lupus-prone mice. Splenic dendritic cells (DCs) from NZB/W F_1 mice spontaneously stimulate nucleosome-specific T cells to a much greater degree than both DCs from normal mice and DCs from the lymph nodes of NZB/W F_1 mice. This leads to a strategy for the local delivery of therapeutic molecules using autoantigen-specific T cells. Nucleosome-specific regulatory T cells engineered by triple gene transfer (TCR-α, TCR-β, and CTLA4Ig) accumulated in the spleen and suppressed the related pathogenic autoantibody production. Nephritis was drastically suppressed without impairing the T cell-dependent humoral immune responses. Thus, autoantigen-specific regulatory T cells engineered by multiple gene transfer is a promising strategy for treating autoimmune diseases. ***The Journal of Immunology,*** **2004, 173: 2118–2125.**

Systemic autoimmune diseases have traditionally been treated using nonspecific immunosuppressive agents, but these agents often lead to opportunistic infections and an increased rate of malignancy. There remains the need to develop selective or specific therapies that target individual autoantigens. Several strategies have been developed as potential Ag-specific immunotherapies, such as using Ag-pulsed dendritic cells (DCs),[3] but the majority of these approaches will require further investigation (1, 2). A more detailed understanding of autoimmune diseases, including autoantigen presentation, is required for the development of reasonable immunotherapies.

Systemic lupus erythematosus (SLE) is a life-threatening autoimmune disease characterized by the production of a variety of autoantibodies (3). Anti-DNA Abs are thought to be one of the major pathogenic products of the autoimmune response (4–6). Datta and colleagues (7–9), as well as other groups (10, 11), have noted that nucleosomes could be a major immunogen for pathogenic autoantibody-inducing T cells in lupus-prone mice. Datta and coworkers (7–9) showed that the majority of pathogenic T_H clones specific for nucleosomes were capable of rapidly inducing anti-DNA autoantibody production, and that these clones were also able to induce nephritis when injected into young lupus-prone mice. Moreover, anti-nucleosome ELISAs have demonstrated better sensitivity, specificity, and diagnostic confidence with regard to human SLE than anti-DNA ELISAs. Anti-nucleosome ELISAs are also correlated with disease activity, as determined by the SLE Disease Activity Index (12, 13).

Although evidences have accumulated demonstrating the importance of nucleosomes as major pathogenic autoantigens, the cellular mechanisms for the immunological recognition of nucleosomes are poorly understood. Generalized hyperresponsiveness of B cells has been reported in both mice and human lupus (14, 15). However, these nonspecific immune disorders cannot provide a sufficient model of nuclear autoantigen-specific autoimmunity encountered in patients with lupus.

To better understand the mechanisms of autoantigen recognition, we first reconstituted nucleosome specificity by TCR gene transfer in $CD4^+$ T cells from (NZB × NZW)F_1 (NZB/W F_1) lupus model mice (3, 16). Using this model, we demonstrated an abnormal autoantigen presentation of splenic DCs. Among the lymphoid organs, this elevated autoantigen presentation of DCs was relatively localized in the spleen. We then developed a triple gene transfer system to generate autoantigen-specific regulatory cells. These regulatory cells preferentially accumulated in the spleen and suppressed the progression of the disease without obvious systemic immunosuppression.

Materials and Methods

Preparation of retroviral construct

Line 3A is a cell line from lupus-prone (SWR × NZB)F_1 (SNF1; I-$A^{d/q}$) that can recognize the immunodominant nucleosomal epitope (histone H4; aa 71–94) in the context of I-A^d (7, 8) and many other I-A molecules (8). Both TCR-α and -β cDNA fragments were synthesized using PCR based on the published sequences of line 3A (7, 8) and designated as AN3 TCR-α and -β. Vα13 and Vβ4 fragments identical to CDR1 and two sequences of line 3A were obtained from NZB splenic cDNA and an added CDR3 sequence by PCR. Jα41-Cα fragment and Jβ2.6-Cβ fragment were also obtained from NZB splenic cDNA and an added CDR3 sequence by PCR. Vα13-CDR3 fragment and CDR3-Jα41-Cα fragment were combined in a

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Received for publication September 24, 2003. Accepted for publication May 12, 2004.

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[1] This study was supported by grants from the Ministry of Health, Labor and Welfare and the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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[3] Abbreviations used in this paper: DC, dendritic cell; SLE, systemic lupus erythematosus; WPRE, woodchuck hepatitis virus posttranscriptional regulatory element; IRES, internal ribosomal entry site; LN, lymph node.

0022-1767/04/$02.00

subsequent "fusion" reaction in which the overlapping ends anneal, allowing the 3′ overlap of each strand to serve as a primer for the 3′ extension of the complementary strand. The resulting fusion product is amplified further by PCR. Vβ4-CDR3 fragment and CDR3-Jβ2.6-Cβ fragment were combined similarly. The full-length fragments were cloned into a pMXW retroviral vector to obtain pMXW-AN3α and pMXW-AN3β (Fig. 1*A*). pMXW is an improved vector generated by insertion of the woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) (17, 18) between the *NotI* and *SalI* sites of pMX (19). WPRE enhances expression of transgenes delivered by retroviral vectors (18), and the expression efficiency of the pMXW vector is improved 1.5 times when WPRE is inserted, compared with the efficiency of the pMX vector. Murine CTLA4Ig cDNA was synthesized by PCR as described previously (20) and was then cloned into the pMX-IRES-GFP (21). Complementary DNAs for the TCR α- and β-chains were isolated from a cDNA library of DO11.10 TCR-transgenic splenocytes and were inserted into the retroviral vector pMX to generate pMX-DOTAE and pMX-DOTBE, respectively (22).

Mice

NZB/W F_1 and BALB/c mice were obtained from Japan SLC (Shizuoka, Japan). All animal experiments were conducted in accordance with the institutional and national guidelines.

Production of retroviral supernatants and retroviral transduction

Total splenocytes were isolated and cultured for 48 h in RPMI 1640 medium supplemented with 10% FCS, 2 mM L-glutamine, 100 U/ml penicillin, 100 μg/ml streptomycin, and 5×10^{-5} M 2-ME in the presence of Con A (10 μg/ml) and IL-2 (50 ng/ml) before the transduction. Retroviral supernatants were obtained by transfection of pMXW, pMXW-AN3α, pMXW-AN3β, pMX-IRES-GFP, pMX-CTLA4Ig-IRES-GFP, pMX-DOTAE, or pMX-DOTBE DNA into PLAT-E packaging cell lines (22, 23) with the use of the FuGENE 6 transfection reagent (Roche Diagnostic Systems, Somerville, NJ).

Falcon 24-well plates (BD Biosciences, San Jose, CA) were coated with the recombinant human fibronectin fragment CH296 (Retronectin; Takara, Otsu, Japan) according to the manufacturer's instructions. Before infection, virus-bound plates were prepared. The viral supernatant (500 μl) was preloaded onto each well of the CH296-coated plate, and the plate was spun at 2000 × *g* for 3 h at 32°C. The virus-coating procedure was repeated three times. Before infection, the viral supernatant was washed away and splenocytes prestimulated for 48 h were added to each well (1×10^6 cells/well). Cells were cultured for 36 h to allow infection to occur. To control the viral expression efficiency, we produced a viral supernatant (pMXW, pMXW-AN3α, pMXW-AN3β, pMX-IRES-GFP, and pMX-CTLA4Ig-IRES-GFP, simultaneously) and prechecked the uniformity of the infection efficiency before in vitro and in vivo experiments.

Cell purification

A $CD4^+$ T cell population was prepared by negative selection with MACS using anti-CD19 mAb, anti-CD11c, mAb, and anti-CD8a mAb. $CD11c^+$ DCs were prepared as previously described (24, 25). Briefly, spleen cells or lymph node cells were digested with collagenase type IV (Sigma-Aldrich, St. Louis, MO) and DNase I, and the $CD11c^+$ cells were selected twice by positive selection using MACS CD11c microbeads and magnetic separation columns. The purity (85% in average) was determined by visualization with anti-CD11c-biotin followed by streptavidin-PE. A $CD19^+$ B cell population was prepared by positive selection with MACS using anti-CD19 mAb. For CFSE labeling (Molecular Probes, Eugene, OR), cells were resuspended in PBS at 1×10^7/ml and incubated with CFSE at a final concentration of 5 mM for 30 min at 37°C, followed by two washes in PBS.

Nucleosome preparation

Pure nucleosomes were prepared as previously described (26). Briefly, frozen pure chicken erythrocytes were thawed and suspended in lysis buffer on ice (10 mM Tris-HCl, 10 mM NaCl, 5 mM $MgCl_2$, 0.5% Nonidet P-40, and 0.25 mM $PhMeSO_2F$, pH 7.5). The nuclei were recovered by centrifugation and the nuclear pellet was washed and digested with micrococcal nuclease. The nuclear pellet was lysed into 0.2 mM Na_2EDTA, and nuclear debris was removed by centrifugation. The soluble chromatin at $A_{260} \approx 100$ was dialyzed against 5 mM triethanolamine HCl, 60 mM NaCl, 1 mM Na_2EDTA (pH 7.5), and subsequently fractionated in the same buffer, usually in sucrose gradients. Gradients were fractionated and monitored at 280 nm, and the appropriate fractions were pooled.

Proliferation assay

At 24 h postinfection, purified $CD4^+$ T cells were cultured at 2×10^4cells/well, with 1×10^5 cells/well of irradiated $CD19^+$ B cells or 1×10^4 cells/well of irradiated $CD11c^+$ DCs in 96-well flat-bottom microtiter plates in volumes of 100 μl of complete medium with or without 1 μg/ml nucleosome or 0.3 μM chicken $OVA_{323-339}$ peptide. After 24 h of culture, the cells were pulse labeled with 1 μCi of [^{3}H]thymidine/well (NEN Life Science Products, Boston, MA) for 15 h and the [^{3}H]thymidine incorporation was determined. In some experiments, we calculated the ratio of (group A − cpm)/(group B − cpm) in each experiment and showed the average ratio of three to five experiments as "average ratio of (group A − cpm)/(group B − cpm) to clarify the reproducibility of the data.

Transfer experiments

The indicated number of cells suspended in PBS were i.v. injected into mice. For the transfer of gene-transduced cells, cell viability was always >97%, as detected by trypan blue exclusion.

ELISA

IgG anti-DNA Abs were quantified using ELISA plates coated with calf thymus DNA (Sigma-Aldrich, and the DNA-binding activities were expressed in units, referring to a standard curve obtained by serial dilutions of a standard serum pool from 7- to 9-mo-old NZB/W F_1 mice, containing 1000 U/ml. IgG antinucleosome Abs or IgG anti-histone Abs were quantified using ELISA plates coated with purified nucleosome or purified histone. Methods for detection of CTLA4Ig protein were described previously (27). Briefly, ELISA plates were coated with anti-mouse CTLA4 (BD PharMingen, San Diego, CA) overnight at 4°C, blocked with blocking solution, and then incubated sequentially for 1 h at 37°°C with serial dilutions of serum or culture supernatants followed by peroxidase-conjugated $F(ab')_2$ goat anti-mouse IgG2a (Accurate Antibodies, Westbury, NY) and ABTS substrate (Kirkegaard & Perry, Gaithersburg, MD). Serial dilutions of a known concentration of purified CTLA4Ig were used in each plate to establish a standard curve.

Histopathology

Organs were fixed in 4% paraformaldehyde, embedded in paraffin, and stained with periodic acid-Schiff solution. For three-color immunofluorescence staining, sections were incubated with biotinylated peanut agglutinin (Vector Laboratories, Burlingame, CA) and then with Cy5.5-conjugated streptavidin (Cortex Biochemicals, Irvine, CA). The sections were then stained with a rat Alexa488-labeled mAb to B220 and tetramethylrhodamine-conjugated mAbs to CD4 and CD8 (Vector Laboratories). To detect the deposition of immune complexes at glomeruli, we incubated sections with FITC-labeled goat Abs to mouse IgG or to C3 (ICN Pharmaceuticals, Costa Mesa, CA).

Statistical analysis

Statistical significance was determined using the unpaired Student's *t* test or the Mann-Whitney *U* test.

Results

Transduction of nucleosome-specific AN3 TCR confers specificity for the nucleosome and autoreactivity to DCs in NZB/W F_1 $CD4^+$ T cells

We previously reported successful TCR gene transfer and reconstitution of the Ag specificity to OVA in BALB/c $CD4^+$ T cells (27). In the present study, we transferred nucleosome-specific TCR genes (AN3α and β) into NZB/W F_1 splenocytes. To improve the expression of the introduced genes, we generated a Moloney-based retroviral vector, pMXW, by insertion of the woodchuck fragment (17, 18) into pMX (19). We selected the TCR of line 3A from lupus-prone SNF1 mice. A hybridoma transfected with this TCR did not exhibit any significant response to either $H\text{-}2^d$ or $H\text{-}2^z$ APCs (28). Each TCR gene was inserted into pMXW, and the resulting retrovirus vectors (pMXW-AN3α and pMXW-AN3β) were used for the gene transfer (Fig. 1*A*).

Retroviral infection of the AN3 TCR genes into NZB/W F_1 splenocytes induced a 40–45% increase in the $V\beta4^+$ population in $CD4^+$ T cells compared with mock-infected splenocytes (Fig. 1*B*). The calculated efficiency of the Vβ4 introduction into the

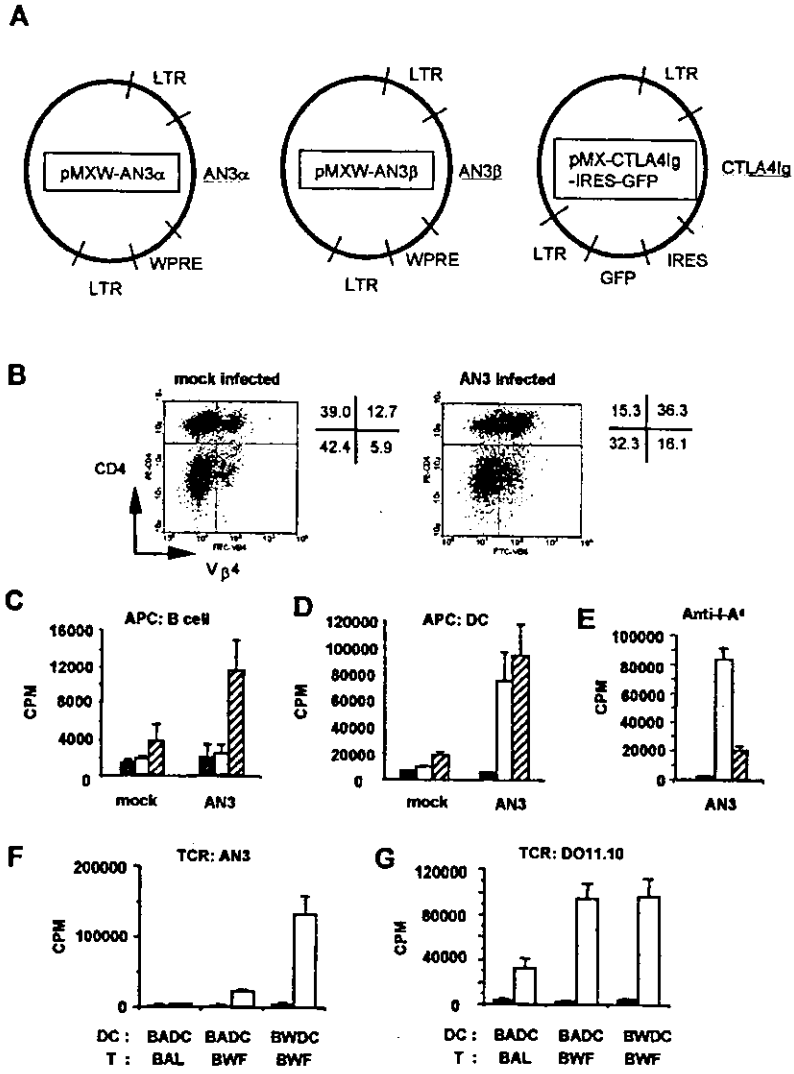

FIGURE 1. Retroviral transfer of AN3 TCR reconstituted the specificity for nucleosomes on NZB/W F_1 $CD4^+$ T cells. Reconstituted T cells showed autoreactivity to splenic DCs. *A*, Schematic representation of the pMXW retrovirus construct expressing the cDNA for the AN3 TCRα or TCRβ chain. LTR, long terminal repeat. *B*, Anti-CD4 and anti-Vβ4 staining of pMXW (mock) or AN3 TCR-transduced NZB/W F_1 splenocytes. Results of a representative experiment are shown. *C*, Proliferation of AN3-transduced and mock-transduced $CD4^+$ T cells to B cells with nucleosomes. ■, T cells alone; □, T + B; ▨, T + B + nucleosomes (1 μg/ml). *D*, Proliferation of AN3-transduced and mock-transduced $CD4^+$ T cells to $CD11c^+$ DCs with nucleosomes. ■, T cells alone; □, T + DCs; ▨, T + DCs + nucleosomes (1 μg/ml). *E*, Blockade of AN3-transduced $CD4^+$ T cell proliferation to NZB/W F_1 $CD11c^+$ DCs by an anti-I-A^d Ab, K24-199. ■, T cells alone; □, T + DCs; ▨, T + DCs + anti-I-A^d Ab. *F*, Proliferative response of AN3- or mock-transduced $CD4^+$ T cells from BALB/c (BAL) or NZB/W F_1 (BWF) (■, mock-transduced cells; □, AN3-transduced cells) with BALB/c $CD11c^+$ DCs (BADC) or NZB/W F_1 $CD11c^+$ DCs (BWDC). *G*, Proliferative response of DO11.10- and mock-transduced $CD4^+$ T cells from BALB/c (BAL) or NZB/W F_1 (BWF) (■, mock-transduced cells; □, DO11.10-transduced cells with 0.3 μM $OVA_{323-339}$) with BALB/c $CD11c^+$ DCs (BADC) or NZB/W F_1 $CD11c^+$ DCs (BWDC). Data shown are representative of more than three independent experiments with similar results.

$CD4^+V\beta4^-$ population was 50–60%. The lack of anti-Vα13 or anti-clonotypic Abs prevented direct visualization of AN3 TCR surface expression. However, based on the transduction of other TCR pairs (i.e., OVA-specific DO11.10 TCR detected by a clonotypic Ab KJ1-26; and AV8/BV7, detectable by anti-Vα8 and anti-Vβ7 Abs; data not shown), we speculate that Vα chain expression is approximately equal to that of the Vβ chain. Thus, the proportion of clonotypic AN3 TCR-expressing cells was estimated to be 25–36% in $CD4^+$ T cells. These cells were referred to as BWF.AN3, and the mock-infected $CD4^+$ T cells were referred to as BWF.mock.

We investigated the specific reactivity to the nucleosomes of BWF.AN3 in the presence of NZB/W F_1 B cells and DCs. Although BWF.mock cells showed minimal proliferation in the presence of B cells and the nucleosomes, BWF.AN3 showed strong proliferation in the presence of B cells and the nucleosomes, but not in the presence of B cells alone (Fig. 1*C*). The average ratio of (BWF.AN3 - cpm)/(BWF.mock − cpm) was 1.13 ± 0.12 and that of (BWF.AN3 with nucleosome (nuc) − cpm)/(BWF.mock with nuc − cpm) was 3.12 ± 0.51 in three experiments ($p < 0.005$). These results demonstrate that the introduction of AN3 TCR reconstitutes the specificity for the nucleosome on $CD4^+$ T cells. Furthermore, BWF.AN3 showed proliferation in the presence of splenic DCs without nucleosome (Fig. 1*D*). The average ratio of (BWF.AN3 − cpm)/(BWF.mock − cpm) was 6.97 ± 1.63 in five experiments ($p < 0.001$). Consistent with previous report that $CD4^+$ T cells of lupus-prone mice responded to nucleosome ex vivo (7), BWF.mock showed relatively weak proliferation in the presence of splenic DCs and nucleosome. The average ratio of (BWF.mock with nuc − cpm)/(BWF.mock − cpm) was 2.21 ± 0.73 in five experiments ($p < 0.05$). Despite these endogenous responses of BWF.mock to nucleosome, BWF.AN3 showed stronger proliferation compared with BWF.mock in the presence of splenic DCs with the nucleosomes. The average ratio of (BWF.AN3 with nuc − cpm)/(BWF.mock with nuc − cpm) was 4.01 ± 2.18 in five experiments ($p < 0.05$).

AN3α-infected or β-infected cells failed to respond to the DCs (data not shown), and the autoreactive response was blocked by anti-I-A^d Ab (Fig. 1*E*). Thus, this autoreactivity of BWF.AN3 to splenic DCs suggests that NZB/W F_1 splenic DCs spontaneously present a considerable amount of nucleosomal epitopes.

The nucleosome-specific response of NZB/W F_1 mice consisted of general T cell hyperreactivity and Ag-specific hyperpresentation of splenic DCs

To investigate the relative contribution of either T cells or splenic DCs to the autoreactive response, we also transduced the AN3 TCR into BALB/c $CD4^+$ T cells and these cells were referred to