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Major pathogenic steps in *human* lupus can be effectively suppressed by nucleosomal histone peptide epitope-induced regulatory immunity

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Abstract Low-dose tolerance therapy with nucleosomal histone peptide epitopes blocks lupus disease in mouse models, but effect in humans is unknown. Herein, we found that $CD4^+CD25^{high}FoxP3^+$ or $CD4^+CD45RA^+FoxP3^{low}$ T-cells, and $CD8^+CD25^+FoxP3^+$ T-cells were all induced durably in PBMCs from inactive lupus patients and healthy subjects by the histone peptide/s themselves, but in active lupus, dexamethasone or hydroxychloroquine unmasked Treg-induction by the peptides. The peptide-induced Treg depended on TGFβ/ALK-5/pSmad 2/3 signaling, and they expressed TGF-β precursor LAP. Lupus patients' sera did not inhibit Treg induction. The peptide epitope-induced T cells markedly suppressed type I IFN related gene expression in lupus PBMC. Finally, the peptide epitopes suppressed pathogenic autoantibody production by PBMC from *active* lupus patients to baseline levels by additional mechanisms besides Treg induction, and as potently as anti-IL6 antibody. Thus, low-dose histone peptide epitopes block pathogenic autoimmune response in human lupus by multiple mechanisms to restore a stable immunoregulatory state.
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Abbreviations: SLE, systemic lupus erythematosus; iTreg, induced regulatory T cells; H, histone; HSCT, hematopoietic stem cell transplantation; LAP, latency associated peptide; DEX, dexamethasone; HCQ, hydroxychloroquine; RA, retinoic acid; $1,25(OH)_2D_3$, 1,25-dihydroxyvitamin D3; RAPA, Rapamycin; APG, Apigenin; TSA, Trichostatin A; ODN, oligonucleotide.

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1. Introduction

Remission maintenance therapy for SLE that specifically targets pathogenic autoimmune cells could prevent recurrence and halt smoldering inflammatory damage. In SLE, cognate interactions between autoimmune T helper (Th) cells and B cells against epitopes from apoptotic nuclear autoantigens lead to production of pathogenic IgG autoantibodies [1–7]. The IgG autoantibodies form inflammatory immune complexes (IC) containing apoptotic cell derived DNA/RNA, and along with CD40L signals from hyperactive lupus T cells, stimulate lupus APC to produce IL-6, IFNα, and other amplifiers of the pathogenic response [8–15].

Five critical autoepitopes in apoptotic cell derived nucleosomes that are recognized by autoimmune T and B cells of *patients* and various mouse strains with SLE are in histone (H) regions, $H1'_{22-42}$, $H3_{82-105}$, $H3_{115-135}$, $H4_{16-39}$ and $H4_{71-94}$ [2,16–19], and these epitopes are promiscuously bound by all major MHC molecules. The peptides delay lupus progression and even restore normal life span, reducing proteinuria in mice with *established* renal disease upon administration in soluble form (tolerization) at high doses intravenously [20]. The peptides are also therapeutically effective when administered intranasally, or in low doses subcutaneously [21–24]. In such lupus-prone mice, tolerance therapy with *nanoMolar* doses of histone peptide epitope/s, which contain both MHC class II and class I binding motifs, induces expansion of potent, autoantigen-specific $CD8^+$, and $CD4^+CD25^+$ regulatory T cell (iTreg) cells which suppress via TGFβ the responses of lupus T cells to nuclear autoantigens, and reduce autoantibody production by inhibiting the T cell help; leading to normal survival span. The stable, autoantigen-specific Treg generated in vivo by the peptide therapy can also block accelerated disease upon adoptive transfer into lupus mice [22]. The therapy especially reduces inflammatory cell reaction in the kidney [22,23]; a major complication of human lupus [25,26]. Only 1 μg (0.34 nM) of the histone peptide epitope/s is effective in low-dose tolerance therapy of mice with lupus, which would be equivalent to 0.2 to 2 mg range in lupus patients. Moreover, similar to the potent CD8 iTreg generated by histone peptide therapy above, or by other autoantigens in mouse models [27–34], we found that in humans, autologous hematopoietic stem cell transplantation (HSCT) for severe lupus also generates identical $FoxP3^+$, LAP^{high} $CD103^{high}$ $CD8^{+}TGF\beta$-producing regulatory T cells (CD8 iTreg), which repairs immunoregulatory deficiency in lupus to maintain patients in *true immunological remission* [19].

Because effect of the nucleosomal peptide epitopes in humans is *unknown*, we studied herein if the histone peptide epitopes have any immunoregulatory effects on lupus patients' autoimmune cells in vitro.

2. Materials and methods

2.1. Subjects

We enrolled 30 lupus patients (10 active and 20 in remission, 22–63 years) who fulfilled the American College of Rheumatology revised criteria for SLE [35], and 15 healthy subjects (23–57 years). Disease activity was scored by the Systemic Lupus Activity Measure index (SLAM) [36]. Patients with SLAM score <7 were considered inactive (remission), and those with SLAM ≥ 7 were considered active. Clinical demographic profile is shown in Table 1. The study was approved by the Institutional Review Board of Northwestern University.

2.2. Cytokines and reagents

IL-2 was purchased from R&D Systems (Minneapolis, MN), TLR9 ligand CPG-containing oligonucleotide (ODN) 2216 was from InvivoGen (San Diego, CA), and anti-IL6 (BD Pharmingen, San Jose, CA), SB-431542 (GlaxoSmithKline, King of Prussia, PA), dexamethasone (DEX), hydroxychloroquine (HCQ), retinoic acid (RA), 1,25-dihydroxyvitamin D3 ($1,25(OH)_2D_3$), Rapamycin (RAPA), Apigenin (APG), and Trichostatin A (TSA) were all from Sigma (St. Louis, MO).

Table 1 Patient demographic: clinical and treatment status of SLE patients in the study. [a]

Patient code	Age/sex/race	SLAM score	Current treatment
1	51/F/C	4	HCQ, SSZ
2	60/F/AA	8	None
3	27/F/AA	7	MMF
4	40/F/H	1	HCQ, Vit D
5	22/F/AA	9	MMF, HCQ, Pred
6	41/F/AA	5	HCQ
7	41/F/C	0	AZT, HCQ
8	24/F/W	15	MMF
9	63/F/C	5	None
10	50/F/C	5	HCQ
11	25/F/AA	2	None
12	32/F/C	1	AZT, HCQ
13	29/M/C	5	MMF, HCQ, Pred
14	50/F/C	2	HCQ
15	63/F/C	3	HCQ
16	34/F/C	2	HCQ
17	43/F/AA	1	HCQ, Pred
18	28/M/H	17	MMF, HCQ, Pred
19	31/F/W	16	AZT, HCQ, Pred
20	40/F/C	5	HCQ
21	43/F/AA	9	HCQ, Pred
22	24/F/H	11	MMF, Pred
23	41/F/C	7	AZT, HCQ, Pred
24	49/F/C	1	HCQ
25	32/F/C	2	HCQ
26	63/M/C	5	HCQ
27	44/M/C	16	HCQ, Pred
28	41/F/C	4	HCQ
29	26/F/A	6	MTX, HCQ, Pred
30	40/F/W	12	Pred, HCQ, MMF

[a] Abbreviations: SLE, systemic lupus erythematosus; SLAM, Systemic Lupus Activity Measure; AA, African American; H, Hispanic; C, Caucasian; F, female; M, male; HCQ, hydroxychloroquine (Plaquenil); Pred., prednisone or steroids; SSZ, sulfasalazine; MMF, mycophenolate mofetil (CellCept); Vit D, vitamin D; AZT, azathioprine; MTX, methotrexate.

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