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Pathways of impending disease flare in African-American systemic lupus erythematosus patients

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ABSTRACT

Immune dysregulation in systemic lupus erythematosus (SLE) contributes to increased disease activity. African-American (AA) SLE patients have an increased prevalence of complications from disease flares and end-organ damage that leads to increased morbidity and early mortality. We previously reported alterations in inflammatory and regulatory immune mediator levels prior to disease flare in European American (EA) SLE patients. In the current study, we assessed baseline and follow-up plasma levels of 52 soluble mediators, including innate, adaptive, chemokine, and TNF superfamily members, in AA SLE patients who developed SELENA-SLEDAI defined flare 6 or 12 weeks after baseline assessment. These patients were compared to themselves during a comparable, clinically stable period (SNF, n = 18), or to demographically matched SLE patients without impending disease flare (NF, n = 13 per group). We observed significant ($q < 0.05$) alterations in 34 soluble mediators at baseline, with increased levels of both innate (IL-1α and type I interferons [IFN]) and adaptive cytokines (Th1-, Th2-, and Th17-type), as well as IFN-associated chemokines and soluble TNF superfamily members weeks before clinical disease flare. In contrast, stable SLE patients exhibited increased levels of the regulatory mediators IL-10 ($q \leq 0.0045$) and TGF-β ($q \leq 0.0004$). Because heterogeneous immune pathways were altered prior to clinical disease flare, we developed a soluble mediator score that encapsulates all mediators tested. This score is the sum of all log transformed, standardized soluble mediator levels assessed at baseline (pre-flare), weighted by their Spearman correlation coefficients for association with the SELENA-SLEDAI score at time of concurrent flare. While baseline SELENA-SLEDAI scores were similar between flare vs. NF ($p = 0.7214$) and SNF ($p = 0.5387$), the SMS was significantly higher in pre-flare SLE patients (Flare vs NF or SNF, $p < 0.0001$). By capturing alterations in the balance between inflammatory and regulatory mediators associated with SLE pathogenesis, the soluble mediator score approximates the immune status of SLE patients and provides a robust, predictive gauge of impending disease flare.

1. Introduction

Systemic lupus erythematosus (SLE) is a prototypical autoimmune disease characterized by chronic immune dysregulation [1]. Disease activity in SLE often waxes and wanes, with flare defined by validated clinical instruments, including the Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI [2]). Despite improved treatment regimens and disease outcomes [3], SLE patients may experience an average of 1.8 disease flares annually [4] that require the use of rapidly acting, potentially toxic agents such as corticosteroids.

The ability to predict impending disease flare would allow for earlier treatment to mitigate or prevent flare-associated organ damage that contributes to increased morbidity and early mortality in SLE patients [5], while also potentially improving quality of life for SLE patients [6]. This would be particularly useful in African-American (AA) SLE patients, who frequently experience a more aggressive disease course. AA SLE patients face an increased risk of developing irreversible organ system involvement, including

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permanent CNS, pulmonary, and cardiovascular damage [7–10], lupus nephritis and end-stage renal disease [11], and a three-fold increase in SLE-related mortality compared to European American (EA) patients [12].

Multiple inflammatory and regulatory mediators are known to be involved in SLE pathogenesis and disease flare, including innate [13] and adaptive cytokines [14], chemokines [15], and altered regulation of soluble receptors [16,17] expressed by activated immune cells. As varied immunological pathways influence disease activity across SLE patient populations, a comprehensive immune mediator panel may be required to monitor immune function and flare risk. Such is the case in rheumatoid arthritis (RA), where a panel of 12 RA-associated soluble mediators has been identified that allows for rapid, reliable, and objective assessment of joint damage risk and response to therapy [18]. In EA SLE patients, we have previously shown that multiple immune mediators change significantly up to 12 weeks prior to disease flare, and that a soluble mediator score (SMS) integrating plasma levels of 52 cytokines and chemokines accurately identifies impending disease flare in EA SLE patients [19]. In the current study, we explored inflammatory and regulatory soluble mediators potentially dysregulated before clinical symptoms of SLE disease flare and tested the ability of the SMS to differentiate impending disease flare in AA SLE patients.

2. Materials and methods

2.1. Study population

Experiments were performed in accordance with the Helsinki Declaration and approved by the Institutional Review Boards of the Oklahoma Medical Research Foundation and the University of Oklahoma Health Sciences Center. Study participants were enrolled in the SLE Influenza Vaccination Cohort [20] after written informed consent. AA SLE patients (meeting $\geq$ 4 ACR classification criteria [20]) with disease flare 6 or 12 weeks post-baseline evaluation (Flare, n = 13) were matched by age (±5 years), race, gender, and time of disease assessment to 13 patients with stable disease (nonflare, NF) and 13 healthy controls (HC). Samples from 18 AA pre-flare SLE patients (Flare) were compared to samples drawn from the same individuals in a different year with no associated SELENA-SLEDAI flare 6 or 12 weeks post-baseline assessment (self non-flare, SNF), as well as 18 healthy controls matched by age (±5 years), race, and gender.

2.2. Clinical data and sample collection

Demographic and clinical information were collected as previously described [20], including humoral response to influenza vaccination, medication usage, clinical laboratory values, disease activity, and SELENA-SLEDAI [2] defined flare (Table 1). SELENA-SLEDAI disease activity was assessed at baseline (pre-vaccination) and again at 6 and 12 weeks post-vaccination (follow-up). The presence of system involvement was evaluated by the administration of the SELENA-SLEDAI disease activity instrument, including the presence of disease manifestations involving the central nervous system (CNS; seizure, psychosis, organic brain syndrome, visual disturbance, cranial nerve disorder, or lupus headache), vasculitis, arthritis, myositis, nephritis (urinary casts, hematuria, proteinuria, or pyuria), mucocutaneous damage (rash, alopecia, or mucosal ulcers), serositis (pleuritis or pericarditis), or hematologic manifestations (low complement, increased DNA binding, fever, thrombocytopenia, or leukopenia) [2]. Blood samples were

Table 1
Demographics and clinical characteristics of African-American (AA) SLE patients.

	Flare (n = 13)	NF[a] (n = 13)	*p-value*	Flare (n = 18)	SNF[b] (n = 18)	*p-value*
Age, mean ± SD years[c]	40.9 ± 10.5	42.7 ± 12.4	*0.3093*	40.5 ± 12.1	40.5 ± 12.6	–
Medications: n positive (%)						
Prednisone[d]	6 (46.1%)	7 (53.8%)	*1.0000*	11 (61.1%)	10 (55.6%)	*1.0000*
Immunosuppressants[d,e]	4 (30.8%)	4 (30.8%)	*1.0000*	6 (33.3%)	9 (50%)	*0.4998*
Hydroxychloroquine[d]	5 (38.5%)	9 (69.2%)	*0.2377*	14 (77.8%)	9 (50%)	*0.1642*
Baseline						
Baseline autoantibody specificities: n positive (%)						
Anti-dsDNA[d]	5 (38.5%)	3 (23.1%)	*0.6728*	6 (33.3%)	2 (11.1%)	*0.2285*
Anti-chromatin[d]	6 (46.2%)	3 (23.1%)	*0.4110*	5 (27.8%)	5 (27.8%)	*1.0000*
Anti-Ro/SSA[d]	2 (15.4%)	2 (15.4%)	*1.0000*	7 (38.9%)	5 (27.8%)	*0.7247*
Anti-La/SSB[d]	1 (7.7%)	1 (7.7%)	*1.0000*	2 (11.1%)	1 (5.6%)	*1.0000*
Anti-Sm[d]	5 (38.5%)	3 (23.1%)	*0.6728*	3 (16.7%)	3 (16.7%)	*1.0000*
Anti-SmRNP[d]	6 (46.2%)	4 (30.8%)	*0.6882*	8 (44.4%)	8 (44.4%)	*1.0000*
Anti-RNP[d]	4 (30.8%)	2 (15.4%)	*0.6447*	5 (27.8%)	6 (33.3%)	*1.0000*
Baseline # of autoantibody specificities: mean ± SD[f]	2.2 ± 2.2	1.4 ± 1.9	*0.3711*	2.0 ± 2.1	1.7 ± 1.7	*0.4609*
Baseline ESR: mean ± SD mm/hour[f]	38.0 ± 18.7	25.7 ± 17.4	*0.2100*	33.7 ± 18.0	28.6 ± 21.9	*0.4609*
Follow-up						
SELENA-SLEDAI score (at follow-up): mean ± SD[c]	7.3 ± 2.9	2.9 ± 3.0	***0.0002***	8.4 ± 6.2	4.1 ± 3.7	***0.0020***
SELENA-SLEDAI organ system manifestations (at follow-up): n positive (%)[d]	12 (92.3%)	6 (46.2%)	***0.0302***	17 (94.4%)	10 (55.6%)	***0.0178***
CNS[d]	0	0	–	1 (5.6%)	0	*1.0000*
Arthritis[d]	8 (61.5%)	5 (38.5%)	*0.4338*	14 (77.8%)	8 (44.4%)	*0.0858*
Renal[d]	1 (7.7%)	0	*1.0000*	0	1 (5.6%)	*1.0000*
Mucocutaneous[d]	8 (61.5%)	2 (15.4%)	***0.0414***	10 (55.6%)	4 (22.2%)	*0.0858*
Serositis[d]	3 (23.1%)	1 (7.7%)	*0.5930*	3 (16.7%)	1 (5.6%)	*0.6026*
Hematalogic[d]	0	0	–	1 (5.6%)	1 (5.6%)	*1.0000*

[a] AA SLE patients with impending SELENA-SLEDAI defined disease flare at follow-up (6 or 12 weeks after baseline) vs. race, gender, and age (±5 years) matched SLE patients who did not experience disease flare over the same time period (non-flare; NF).
[b] AA SLE patients with impending disease SELENA-SLEDAI defined disease flare at follow-up (6 or 12 weeks after baseline) vs. the *same* SLE patients during a year of the study without disease flare (self non-flare; SNF).
[c] Statistical significance determined by paired t-test.
[d] Statistical significance determined by Fisher's exact test; $\boldsymbol{p \leq 0.05}$.
[e] Immunosuppressants = azathioprine, mycophenolate mofetil, cyclophosphamide.
[f] Statistical significance determined by Wilcoxon's matched pairs test.