Abstract 801 Table 1 Adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for SLE flare across sub-cohorts

Characteristics at time zero	Sub-cohort I, HCQ reduced	Maintenance (matched to I)	Sub-cohort II, HCQ discontinued	Maintenance (matched to II)
	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
Male sex	1.04 (0.74, 1.45)	0.93 (0.68, 1.29)	0.94 (0.62, 1.42)	0.88 (0.61, 1.27)
Non-Caucasian race/ethnicity	1.19 (0.94, 1.51)	1.01 (0.81, 1.26)	0.95 (0.69, 1.29)	1.18 (0.91, 1.54)
Age at SLE diagnosis, years	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	0.99 (0.98, 1.00)	1.01 (1.00, 1.02)
No post-secondary education	1.04 (0.85, 1.28)	1.16 (0.95, 1.43)	1.40 (1.07, 1.83)	0.90 (0.70, 1.15)
Geographic location				
North America	Reference	Reference	Reference	Reference
Europe	1.16 (0.91, 1.48)	1.10 (0.87, 1.40)	1.03 (0.76, 1.39)	1.05 (0.80, 1.37)
Asia	0.69 (0.51, 0.93)	0.87 (0.61, 1.23)	0.68 (0.46, 1.02)	0.66 (0.43, 0.99)
SLE duration	1.02 (0.98, 1.06)	1.00 (0.96, 1.04)	0.99 (0.95, 1.04)	0.99 (0.95, 1.03)
SLEDAI-2K ≥ 4	1.15 (0.94, 1.41)	1.17 (0.94, 1.44)	1.18 (0.90, 1.54)	1.17 (0.92, 1.48)
Renal damage	0.90 (0.60, 1.37)	0.99 (0.62, 1.59)	0.81 (0.55, 1.21)	0.82 (0.48, 1.39)
Body mass index	1.02 (1.00, 1.04)	1.00 (0.98, 1.01)	0.99 (0.97, 1.02)	0.99 (0.97, 1.01)
Smoker	1.07 (0.85, 1.35)	0.98 (0.78, 1.22)	0.95 (0.72, 1.25)	1.09 (0.83, 1.43)
Prednisone	1.63 (1.28, 2.09)	2.03 (1.59, 2.59)	1.79 (1.31, 2.44)	2.39 (1.79, 3.19)
Immunosuppressive	1.60 (1.28, 2.00)	2.34 (1.87, 2.92)	1.48 (1.09, 2.01)	2.42 (1.86, 3.16)
Biologics	0.67 (0.36, 1.24)	0.88 (0.47, 1.67)	0.63 (0.32, 1.26)	0.94 (0.45, 1.98)

was 43.1 (95% CI 38.3, 48.4), versus 34.2 (95% CI 30.6, 38.2) in the matched maintenance sub-cohort. Table 1 shows the factors associated with time to flare within each sub-cohort. The hazard ratios are adjusted by all variables in the table. Prednisone or immunosuppressive use at time-zero was associated with higher flare risk in all analyses. Lower education was associated with higher risk of SLE flares among patients who discontinued HCQ. There was a trend across sub-cohorts for lower flare risk among patients from Asia, versus North America.

Conclusions Compared to HCQ maintenance, crude flare rates were numerically higher after HCQ taper/discontinuation. SLE patients on prednisone or immunosuppressives were at higher risk for flare in all groups. The association between lower education and higher SLE flare risk was most clearly seen upon discontinuation of HCQ, suggesting this as a particularly vulnerable group.

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900 – Nucleic acids in SLE

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AUTOANTIBODY-MEDIATED IMPAIRMENT OF DNASE1L3 ACTIVITY IN SPORADIC SYSTEMIC LUPUS ERYTHEMATOSUS

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Background Antibodies to double-stranded DNA are prevalent and pathogenic in systemic lupus erythematosus (SLE), particularly in patients with lupus nephritis. However, the physical

nature and regulation of cell-free DNA (cfDNA) that becomes antigenic in SLE is poorly understood. Null mutations in the secreted DNase DNASE1L3 cause human monogenic SLE with anti-dsDNA autoreactivity, whereas a hypomorphic variant of DNASE1L3 is associated with SLE and other autoimmune diseases. We sought to characterize the role of DNASE1L3 in the regulation of cfDNA and its relevance for sporadic forms of SLE that are not associated with DNASE1L3 variants or mutations.

Methods Activity of DNASE1L3 in the plasma of SLE patients was measured using a novel assay based on the digestion of intact cell nuclei. Antibodies to DNASE1L3 were measured using a novel ELISA with recombinant DNASE1L3 as an antigen. The fraction of microparticle-associated cell-free DNA was measured using differential centrifugation followed by genomic qPCR. Antibodies to DNASE1L3-sensitive antigens on microparticles were measured by flow cytometry using tissue culture-derived microparticles digested with recombinant DNASE1L3.

Results More than 50% of sporadic SLE patients with nephritis manifested reduced DNASE1L3 activity in circulation. This reduced activity was associated with the presence of neutralizing autoantibodies to DNASE1L3, but not to its close homolog DNASE1. Patients with reduced DNASE1L3 activity had normal total plasma cfDNA levels but showed accumulation of cfDNA in circulating microparticles released from apoptotic cells. Microparticle-associated cfDNA contained a higher fraction of longer polynucleosomal cfDNA fragments, which bound autoantibodies with higher affinity than mononucleosomal fragments and were stronger inducers of type I interferon. Autoantibodies to DNASE1L3-sensitive antigens on microparticles were prevalent in SLE nephritis patients and correlated with the accumulation of cfDNA in microparticles and with disease severity. DNASE1L3-sensitive antigens on microparticles included DNA-associated proteins such as HMGB1, a known self-antigen in SLE.

Conclusions Our results suggest that autoantibody-mediated impairment of DNASE1L3 activity is a common non-genetic mechanism facilitating anti-dsDNA autoreactivity in patients with severe sporadic SLE. In particular, it leads to the

accumulation of longer polynucleosomal DNA fragments in circulating microparticles, and to autoantibody responses to microparticle-associated DNA and protein antigens.

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REGULATORY RNAs IN NEUROPSYCHIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

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Background Brain-specific Cytoplasmic (BC) RNAs operate as translational regulators at neuronal synapses. BC RNAs are delivered to synapto-dendritic sites of function by transport factors heterogeneous nuclear ribonucleoprotein A2 (hnRNP A2) and Pur α . Dysregulation of BC RNA control has been associated with epilepsy and cognitive impairment. We hypothesized that structural motifs in BC RNAs can become targets of autoimmune reactivity in neuropsychiatric SLE.

Methods Sera were collected from patients with SLE, rheumatoid arthritis (RA), multiple sclerosis (MS), and from healthy subjects (HS).¹ RNA-protein interactions were examined by electrophoretic mobility shift assays (EMSAs). Microinjection RNA transport analysis was performed with sympathetic neurons in primary culture. Sera or purified antibodies were injected i.v. into wild-type (WT) mice, in conjunction with i.p. injection of lipopolysaccharide to permeabilize the blood-brain barrier.²

Results Autoantibodies against BC RNAs (anti-BC abs) were detected in a subset of SLE patient sera. Strength of SLE anti-BC autoimmune reactivities and occurrence of neuropsychiatric manifestations, in particular seizures, correlated

strongly (Spearman's $r_s = 0.89$, $P < 0.0001$). Anti-BC abs were not detected in sera from RA or MS patients or in sera from HS. In human BC200 RNA, a noncanonical dendritic targeting element (DTE) is responsible for binding of transport factors hnRNP A2 and Pur α and for specifying delivery to synapto-dendritic domains. The same DTE is complexed by SLE anti-BC abs with high affinity and essentially irreversibly, in interactions that cause displacement of transport factors and inhibition of synapto-dendritic transport.

Lack of BC RNAs in neurons, either cell-wide or locally at the synapse, causes seizure susceptibility and cognitive impairment.³⁻⁵ We posited that introduction of SLE anti-BC IgGs into the brains of naïve WT mice, which causes BC RNA dendritic transport inhibition and thus depletion at the synapse, would result in analogous phenotypes. Indeed upon auditory stimulation, such mice succumbed to severe generalized tonic-clonic seizures (seizure rate 100%, mortality 100%). Mice injected with non-SLE IgGs (RA, MS, HS) never seized. Significantly, when SLE anti-BC IgGs were coinjected with human BC200 RNA, seizures did not materialize (Fisher's Exact Test, $P < 0.0001$).

Conclusions Our data show that SLE anti-BC IgGs, isolated from sera of lupus patients with a history of seizures, cause severe seizures in animals. Seizures are completely prevented if SLE anti-BC IgGs are complexed with BC200 RNA. We propose that this approach may lend to the development of therapeutic interventions using BC200 decoys.

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1000 – Patient-reported outcomes

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LONGITUDINAL CHANGES IN TYPE 2 SLE ACTIVITY

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Background The Type 1 & 2 SLE Model categorizes signs and symptoms as Type 1 (arthritis, nephritis, and rash) and Type 2 (fatigue, brain fog, and widespread pain). It is currently unknown whether Type 2 SLE symptoms vary over time. In this study, we measured longitudinal changes in Type

Abstract 902 Figure 1 SLE anti-BC abs: molecular – cellular mode of action. SLE anti-BC abs target transport-specifying DTEs in BC RNAs (here represented by rodent BC1 RNA; Scene 1). They prevent binding of hnRNP A2 (and Pur α , not shown) to such DTEs (which occurs normally in the absence of SLE anti-BC abs; Scene 2). Dendritic delivery of BC RNAs (Scene 3) is thus compromised by SLE anti-BC abs. Lack of BC RNAs at the synapse results in aberrant local translational control ((due to unbalanced metabotropic glutamate receptor stimulation of synaptic translation; Scene 4), causing network hyperexcitability and consequential phenotypic alterations. From ref. [1].