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 ERYTHEMATOUS (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 (hnRNPA2) and Purα. 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). RNA-protein interactions were examined by electrophoretic mobility shift assays (EMSA). Microinjection transport RNA 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.

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 rs = 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 hnRNPA2 and Purα 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.1-5 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

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
2 SLE activity as measured by the Polysymptomatic Distress (PSD) Scale.

Methods Lupus patients meeting ACR or SLICC criteria in a university lupus registry completed the PSD. SLEDAI scores were also recorded. Patients with ≥2 clinical visits over a 52-week period were included. Groups were selected based on mean, indicating severity of symptoms, and the standard deviation, indicating variability of symptoms, of PSD scores across visits. Differences across groups were assessed with chi-square and ANOVA tests.

Results The study included 204 patients. Four Type 2 SLE activity groups were identified (figure 1): chronic low (n=71; 35%), variable low (n=31, 15%), chronic high (n=31, 15%), and variable high (n=71, 35%).

Patients in the chronic low and variable low Type 2 groups had similar demographics, with two-thirds being black and 54 and 68%, respectively, having a history of nephritis. The chronic low Type 2 group had stable minimal Type 2 SLE, with an average PSD score of 3.7 that ranged from 2.8 to 4.7. Similarly, these patients had minimal Type 1 SLE activity, with average clinical SLEDAI scores of 0.7. The variable low Type 2 group had higher PSD scores (average: 4.5), ranging from 1.8 to 7.7, as well as higher SLEDAI scores than the chronic low Type 2 group, with ~25% having a SLEDAI ≥8.

Patients in the chronic high and variable high Type 2 groups also had similar demographics with half being black and two-thirds having no history of nephritis. Additionally, both groups had average SLEDAI scores of 4. Patients in the chronic high Type 2 group had stable high PSD scores ranging on average from 10.3 to 12.7. Patients in the variable high Type 2 group had average scores of 14.1 with a larger range: 10 to 18.5.

Conclusion These findings indicate that patients with lupus differ in their Type 2 SLE activity. One-third of patients had constant high Type 2 activity, and about half had fluctuating Type 2 symptoms. Future studies will determine if this fluctuation is due to inflammation or non-inflammatory etiologies such as perceived stress, extent of social support, PTSD, illness perception, or resilience factors.