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

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902 REGULATORY RNAS IN NEUROPSYCHIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

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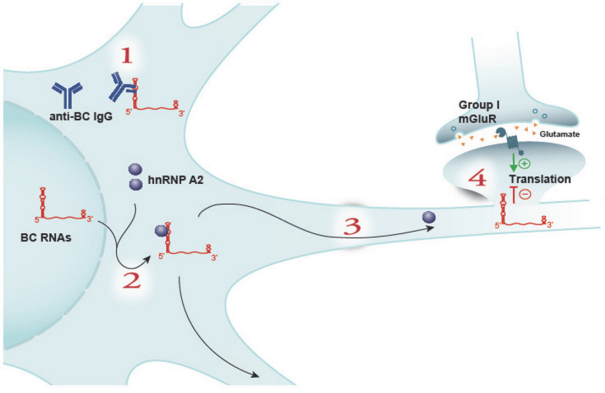
Background Brain-specific Cytoplasmic (BC) RNAs operate as translational regulators at neuronal synapses. BC RNAs are delivered to synapto-dendritic sites of function by transport factors heterogeneous nuclear ribonucleoprotein A2 (hnRNP A2) and Purα. Dysregulation of BC RNA control has been associated 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).[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 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.



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 Purα, 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].

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

1001 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