The active intrathecal B-cell response in LGI1-antibody encephalitis.

Abstract:
Leucine-rich glioma inactivated 1 (LGI1) is a component of the voltage-gated potassium channel complex. IgG antibodies against LGI1 are associated with immunotherapy-responsive encephalitis and epilepsies. LGI1-antibody concentrations are 10-100 times greater in serum than in cerebrospinal fluid (CSF). Oligoclonal IgG bands are rarely found in patients with LGI1-antibody encephalitis or epilepsy. These observations raise questions about the sources of the B cells that result in production of LGI1 antibodies and how the IgGs reach the brain. We aimed to investigate the migration and expansions of peripheral and central B cells to the production of LGI1-specific IgG. We performed PCR amplification and next generation deep immune repertoire sequencing of immunoglobulin (Ig) heavy chain variable regions (VH) from CSF and subsorted peripheral blood B-cell populations from two patients with limbic encephalitis and faciobrachial dystonic seizures associated with LGI1 antibodies. Bioinformatics clustering of related IgM-VH or IgG-VH transcripts was used to determine whether active B-cell diversification could be observed, and whether intrathecal B-cell repertoires, if present, were related to peripheral B cells. We identified clusters of related Ig-VH transcripts in the CSF of both patients. Within these clusters there was a range of somatic hypermutations
along the IGHV germline segment-derived portion. In addition, we identified a large number of closely related Ig-VH clusters that were common to both CSF and peripheral blood, including a small number of dominating Ig-VH clusters that might represent the most active clonally related B-cell populations. Our data suggest that some B-cell affinity maturation occurs inside the CNS compartment in LGI1-antibody encephalitis. Somatic hypermutation rates point to a CSF antigen-driven activation of clonally related B cells that shape the intrathecal immune repertoire. The target antigen or antigens of these clonally related B cells remain unknown; our work continues to determine the relative contribution of intrathecally activated and peripheral LGI1-specific B cells in this autoimmune CNS disease. Wellcome Trust Intermediate Fellowship to SRI, Fulbright-MS Society, Epilepsy Research UK, BMA Vera Down Research Grant.

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