Development of a new Neuromyelitis Optica model mice

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Background

Neuromyelitis Optica (NMO) is a severe neuroinflammatory autoimmune disease of the CNS accompanied by demyelination, mainly affecting the spinal cord and optic nerves. It is characterized by autoantibodies (NMO-IgG) targeting the extracellular domains of aquaporin-4 (AQP4), which is the most reliable marker to diagnose a patient having NMO. AQP4 is predominantly expressed on perivascular endfeet of astrocytes. Thus, it is widely accepted that binding of NMO-IgG to AQP4 results in complement-dependent disruption of astrocytes, which leads to demyelination. However, a mechanism connecting the disruption of astrocytes to demyelination is still unclear. A comprehensive NMO rodent model has not been established to replicate the immune response in the CNS. Models are required for understanding the mechanism of the disease and assess the efficacy of potential therapies.

Methods

To temporally control expression of AQP4, CreERT2 expressing C57BL/6J and BALB/c mice harboring a floxed cassette in exon 0 of the AQP4 gene, which abolished AQP4 expression, were established. Prior to the induction of AQP4, to present AQP4 as an antigen, subject mice were immunized intraperitoneally with approximately 10 million WT astrocytes on days 0 and 14 with 500 ng of pertussis toxin on days 0 and 2. Beginning from day 17, subject mice were injected intraperitoneally with 5 rounds tamoxifen (9 mg/40 g B.W.) every other day. On day 46, mice were sacrificed to collect sera for assessment of plasma anti-AQP4 antibody level by ELISA and some tissues, including cerebella, spinal cords, and kidneys, for checking induced AQP4 by histological analysis as well as Western blotting.

Results

Using ELISA, we confirmed that sera of immunized and tamoxifen-injected subject mice showed significant and sustained production of anti-AQP4 IgG, regardless of strain. Immunohistochemistry of subject mice demonstrated that tamoxifen induced moderate AQP4 expression in kidney, brain and spinal cord compared to WT mice.

Conclusions

We have developed mice possessing endogenously generated anti-AQP4 IgG, in which we can induce expression of AQP4 by tamoxifen treatment. These mice are a potential model mimicking autoimmunity against AQP4 and useful to understand NMO pathology.