

## **Aquaporin 4 and Neuroinflammation**

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The role of auto-antibodies to aquaporin 4 (AQP4) in neuromyelitis optica was first suggested by studies in which human sera was reacted with mouse tissue sections. Sera from patients with NMO showed a pattern of immunoreactivity that highlighted CNS microvessels and the pia (Lennon et al., 2004). This and the pattern of immunoreactivity in kidney and stomach suggested that AQP4 was the target antigen, and this was proven to be the case (Lennon, et al., 2005). Studies on tissue from NMO patients showed that there is loss of AQP4 immunoreactivity and complement deposition in the lesions of inflammatory demyelination, but not in uninvolved tissue. At the time, AQP4 was known to be the predominant water channel in the brain and had a role in brain edema formation in response to a variety of etiologies. The possible involvement of AQP4 in neuroinflammation had never been investigated. Several groups explored the pathogenic role of antibodies to AQP4 in rodent models (see Li et al. 2011 for references). These studies showed that administration of anti-AQP4 antibodies to animals with EAE or along with complement to naïve animals produced pathology characteristic of NMO. When EAE was induced in AQP4 knockout mice, the animals had attenuated symptoms and CNS inflammation compared to wild-type controls. This group went on to perform a systematic exploration of the mechanism by which AQP4 deficiency protected animals from the inflammatory pathology of EAE (Li et al., 2011). The major difference between the two groups was that the knockout mice showed a decreased inflammatory response to intracerebral injection with lipopolysaccharide (LPS). In vitro analysis of microglia-free astrocyte cultures showed that LPS induced secretion of TNF-alpha and IL-6 into the medium, but this was reduced in the knockout animals compared to controls. Transfection studies demonstrated that cytokine

secretion was directly related to expression of AQP4 by cells. These recent data provide new hypotheses for investigating the role of the water permeability function of astrocytes in neuroinflammation.

### **References**

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