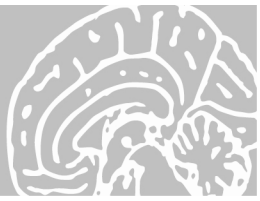
Neuromyelitis optica: an antigen-specific disease



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Neuromyelitis optica (NMO) is an autoimmune disease that preferentially targets the optic nerve, brainstem and spinal cord leading to blindness and paralysis associated with a serological biomarker antibody against the aquaporin-4 (AQP4) water channel. No other autoimmune disease specifically targets AQP4, a water channel expressed on astrocytes in the CNS. We recently developed an NMO mouse model that confirmed the specificity of the immune attack on AQP4 by demonstrating that pathogenic T cells targeting AQP4 cause optic neuritis and transverse myelitis. The clinical manifestation of blindness and paralysis in the mouse correlated with extensive inflammatory infiltrates in the optic nerves and spinal cord. Interestingly, although these cells were transferred intravenously, there was no inflammation in non-CNS organs despite AQP4 expression, such as the lungs and kidneys, which recapitatules human NMO disease.

Our mouse model reproduces several aspects of the human disease that may provide insight into the immunopathogenesis of NMO. One of the timeless questions about NMO is why does this disease preferentially targets the spinal cord and optic nerve, as well as the brainstem? It cannot simply be explained by the expression pattern of AQP4 because AQP4 is expressed throughout the brain, as well as the lung, kidney, stomach, heart, lymphocytes and just about every tissue in the body. In our mouse model of NMO, T cells against AQP4 are injected into the tail vein and yet 8 days later, they invade the optic nerves and spinal cord while sparing all other AQP4-expressing organs, just as in the human NMO disease. Thus, understanding our animal model may help to answer this question about the localization of NMO in humans. A second burning question about NMO is what triggers an attack of the CNS? In our mouse model, AQP4-reactive T cells injected peripherally initiate an attack of optic neuritis exactly 8 days later. Understanding what these T cells are doing and who they are interacting with during those 8 days may explain how T cells are triggered to attack in humans with NMO. The third question about NMO is can the immune system be re-educated not to attack AQP4? Our animal model suggests that since AQP4-reactive T cells are sufficient to cause the disease, they are an ideal target for tolerization therapy. Tolerization therapy, also known as anergy induction, is aimed at suppressing the pathogenic effects of T cells by stimulating their T cell receptors with antigen, but doing so in the absence of co-stimulation, which has the effect of inducing T cell apoptosis instead of activation. We will use our model to develop a tolerization therapy that can be directly translated to the clinic. Studying this mouse model of NMO will yield important insights into the pathogenesis of human NMO disease and help to answer some of the most pressing questions in the field. More importantly, we can use this information to develop specific treatments to switch off the reaction to AQP4, permanently.