Potassium channel KIR4.1 as an immune target in multiple sclerosis.

Abstract:
Multiple sclerosis is a chronic inflammatory demyelinating disease of the central nervous system. Many findings suggest that the disease has an autoimmune pathogenesis; the target of the immune response is not yet known. We screened serum IgG from persons with multiple sclerosis to identify antibodies that are capable of binding to brain tissue and observed specific binding of IgG to glial cells in a subgroup of patients. Using a proteomic approach focusing on membrane proteins, we identified the ATP-sensitive inward rectifying potassium channel KIR4.1 as the target of the IgG antibodies. We used a multifaceted validation strategy to confirm KIR4.1 as a target of the autoantibody response in multiple sclerosis and to show its potential pathogenicity in vivo. Serum levels of antibodies to KIR4.1 were higher in persons with multiple sclerosis than in persons with other neurologic diseases and healthy donors (P<0.001 for both comparisons). We replicated this finding in two independent groups of persons with multiple sclerosis or other neurologic diseases (P<0.001 for both comparisons). Analysis of the combined data sets indicated the presence of serum antibodies to KIR4.1 in 186 of 397 persons with multiple sclerosis (46.9%), in 3 of 329 persons with other neurologic diseases (0.9%), and in none of the 59 healthy donors. These antibodies bound to the first extracellular loop of...
KIR4.1. Injection of KIR4.1 serum IgG into the cisternae magnae of mice led to a profound loss of KIR4.1 expression, altered expression of glial fibrillary acidic protein in astrocytes, and activation of the complement cascade at sites of KIR4.1 expression in the cerebellum. KIR4.1 is a target of the autoantibody response in a subgroup of persons with multiple sclerosis. (Funded by the German Ministry for Education and Research and Deutsche Forschungsgemeinschaft.).