A sphingosine-1-phosphate receptor 1-directed agonist reduces central nervous system inflammation in a plasmacytoid dendritic cell-dependent manner


Gradients of the sphingolipid sphingosine-1-phosphate (S1P) are responsible for the egress of lymphocytes from lymph nodes by activating the S1P1 receptor expressed on the surface of lymphocytes. Small molecule drugs that downregulate S1P receptors induce the sequestration of lymphocytes within lymph nodes, thus preventing lymphocytes from accessing sites of inflammation. In particular, FTY720, a pan-S1P receptor agonist, has been efficacious in the treatment of multiple sclerosis as well as its animal model, experimental autoimmune encephalomyelitis (EAE), by virtue of its ability to restrain lymphocytes within the lymph nodes, thus precluding their migration into the CNS. However, multiple leukocyte subsets express S1P receptors of varying types, and although it is beneficial to prevent transmigration of proinflammatory lymphocytes into the CNS, allowing access of regulatory leukocyte subsets to the CNS is desirable. In this study, we show that an S1P1-specific agonist (AUY954) is clinically efficacious in ameliorating pre-established EAE in SJL/J mice. Efficacy of AUY954 correlated with a reduction of lymphocytes in the CNS, but access of plasmacytoid dendritic cells (pDCs) to the CNS was unimpaired, and the presence of pDCs was found to be an important cofactor in mediating the clinical efficacy of AUY954. These results indicate that pDCs are important in quieting autoimmune responses during EAE, and that trafficking inhibitors that are permissive for pDC accumulation in the CNS may be of therapeutic value for the treatment of multiple sclerosis.