THE ANTIPROLIFERATIVE GENE TOB1 IS INVOLVED IN MULTIPLE SCLEROSIS AND EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS PATHOGENESIS

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We recently identified a gene expression signature in CD4+ T cells of individuals with clinically isolated syndrome (CIS) that highly correlated with a rapid progression to multiple sclerosis (MS). This signature included up-regulation of genes that promote T-cell activation as well as down-regulation of genes that promote quiescence. Among these, the antiproliferative gene TOB1 was 7-fold downregulated. We hypothesized that Tob1-deficient mice will show an earlier disease onset, a more severe phenotype, or both. We then set out to characterize the immunologic and neurodevelopmental properties of Tob1-/- animals.

We used Tob1-/- mice to assess the effects of this gene in experimental autoimmune encephalomyelitis (EAE) pathogenesis. We also conducted immunologic studies to characterize the properties of Tob1-/- T cells. In addition, we tested the effect of the histone deacetylase inhibitor (HDAC) TSA to suppress EAE. Tob1-/- mice experienced both an earlier onset and a more severe EAE. Analysis of motoneuron function and apoptosis suggest that the earlier onset is associated with neural toxicity in the Tob1-/- animals. Tob1-/- T cells proliferate more and express more IL-17 and IL-23 than their WT counterparts. Tob1-/- mice showed a significant delay in spinal cord myelination at P5 compared with WT mice. Finally, we found that the HDAC inhibitor TSA (which increases Tob1 expression by >10-fold in vitro) ameliorated EAE. Strikingly, Tob1-/- animals showed no improvement, suggesting that Tob1 expression is required for the beneficial effects of TSA. We confirmed these results with in vitro experiments.

Our results suggest a dual role of Tob1 in the central nervous system and the periphery. We found that while Tob1 is required for keeping quiescence in T cells in the periphery, it may also be critical for oligodendrocytes to (re)myelinate axons in a timely manner. Tob1 is required for TSA to exert its beneficial effect in EAE and to suppress T-cell proliferation in vitro.