Multiple Sclerosis and Epilepsy: Insights into a Potential Therapy Through the Role of Mutation T1244C of Theiler's Murine Encephalomyelitis Virus (TMEV) in Reducing Virulence

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TMEV, a murine single-stranded positive sense RNA virus, is a model for both multiple sclerosis (MS) and epilepsy, as it results in a demyelinating encephalomyelitis in the CNS, resembling MS, and epilepsy in C57BL/6 mice. Previous research conducted on two variants of TMEV DA strain, C and D, showed that DA-D, which produces extensive demyelination in mice despite its smaller plaque size, caused extensive neuronal damage and encephalomyelitis, as opposed to DA-C, which is significantly less virulent in both models. The genomes of DA-C and DA-D were completely sequenced through RT-PCR sequencing. One plausible coding mutation T1244C in the leader polyprotein was found between DA-C and DA-D. Through site-directed mutagenesis, T1244C was inserted into the plasmid backbone, new virus was grown and harvested, and plaque assays were performed to determine virus titre and plaque sizes. As predicted, large plaque sizes resulted- similar to DA-C. Then, C57BL/6 mice were injected intracranially with the mutated virus, DA-D, and a sham to characterize the phenotypic effects of the viruses. Supporting the initial hypothesis, the leader mutation was attenuating, as mice infected with the mutated virus exhibited lower levels of demyelination, perivascular cuffing, edema, and overall virulence- especially in comparison to DA-D, which was the variant with the most severe effects. The purpose was to outline the role of the T1244C mutation in decreasing virulence in C57BL/6 mice, and its potential as a future therapy for MS and epilepsy due to the fact that TMEV is an uncannily accurate model for the human diseases.

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