Specificity and phenotype of T cells in MS lesions

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Research question and background

The complex etiology of multiple sclerosis (MS) involves both a genetic predisposition and environmental factors, among which Epstein Barr virus infection is dominant. Recent studies have indicated an important role of CD8 T-cells in the initiation and perpetuation of the lesions in this neurodegenerative autoimmune disease. However, we previously demonstrated that CD8 T-cells controlling HSV-1 latency in sensory neurons located in trigeminal ganglia (TG) cause no immune-pathology. We aim to characterize the phenotype and antigen-specificity of CD8 T-cells recovered from the cerebral spinal fluid (CSF), TG and brain tissues of MS patients.

Methods and tissues used

The acquisition of paired MS brain lesions, normal appearing white matter (NAWM), CSF, TG and blood with short to medium post-mortem intervals offers the unique opportunity to compare the phenotype and specificity of CD8 T-cells derived from each anatomic location. T-cell lines (TCLs) were generated analogously from "viable" tissues from deceased MS patients (n=15). Parts of the brain tissues were snap-frozen for in-situ analysis and parts were dispersed for flowcytometric analysis. Autologous EBV transformed B-cell lines (BLCLs) are generated to be used as antigen presenting cells in functional T-cell assays to determine T-cell reactivity to EBV- and potential MS-associated neuro-antigens (i.e. CryAb, CNTN2, KIR4.1, MAG, 2 isoforms of MBP, MOG, NF155, PLP1 and S100B) using episomally replicating expression vectors.

Results and conclusions

In-situ analysis show MS lesions containing extravasated T-cells, both CD4 and CD8, in proximity of damaged areas. Ki67 and granzyme B expression was restricted to extravasated T-cells. Flow cytometric analysis shows that intra-lesional CD8 outnumber CD4 T-cells and are almost exclusively of an effector memory phenotype. Interestingly, both intra-lesional and NAWM T-cells show increased activation (CD95L, CD137 and ICOS) compared to blood. No reactivity to neuro-antigens was detected in MS lesion-TCL but 2 of 5 analyzed patient showed elevated EBV-specific CD8 T-cell reactivity in the MS lesion compared to control tissues. This elevated EBV CD8 T-cell response indicates a perpetuating role in MS pathology.