The IGHG1 alleles determine the B cell repertoires in the cerebrospinal fluid of patients with multiple sclerosis

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Background: B cells are enriched in the brain and the cerebral spinal fluid (CSF) of multiple sclerosis (MS) patients, and a limited number of isotype-switched B cell clones dominate the CSF. Single-cell transcriptomics and bioinformatics have made it possible to link the B-cell receptor heavy- and light-chain sequences to the complete immunoglobulin alleles.

Methods: We used single-cell RNA-seq technology on B cells from the CSF of 11 treatment-naïve MS patients. Single-cell sorted CD3–CD14–CD16–CD27++CD38++ plasmablasts and CD3–CD14–CD16–CD19+ cells from the CSF were processed using a modified Smart-Seq2 protocol, and the full transcriptome of each cell was sequenced on Illumina NextSeq500 platform. The data were analysed using BraCeR.

Results: We found that plasmablasts in the CSF of MS patients were clonally expanded and showed a higher degree of clonal relatedness than expected from previous studies using bulk sequencing. Single-cell transcriptome analysis showed a predominance of the IgG1 isotype among plasmablasts, but expanded IgM and IgA clones were also found. In MS patients heterozygous for the IGHG1*01 and *03 alleles, the IGHG1*01 expressing cells dominated strongly over the IGHG1*03 expressing cells. A biased usage of VH4 gene segments and κ light chain was only observed in plasmablasts among patients carrying the IGHG1*01 allele. Patients homozygous for the IGHG1*03 allele, on the other hand, showed an increased usage of the VH1 and VH3 gene segments and lambda light chain. In patients carrying the IGHG1*01 allele, VH4 frequently paired with KV1 family genes, whereas no preferential pairing of heavy and light chain genes was observed in patients homozygous for the IGHG1*03 allele.

Conclusion: A preferential pairing of VH4 gene segments with kappa light chain genes in plasmablasts of MS patients is associated with the IGHG1*01 allele. This suggests that the intrathecal humoral immune response is qualitatively different in patients carrying the allele.