

## Differential response to cerebral cortex demyelination of oligodendrocyte lineage cells during chronic course of experimental autoimmune encephalomyelitis

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Experimental autoimmune encephalomyelitis (EAE) is an animal model of Multiple Sclerosis (MS) that shares many features with the human autoimmune demyelinating disease. The most commonly studied EAE models are characterized by acute and reversible demyelination. The chronic forms of EAE are less studied and evidence of demyelination in EAE cerebral cortex is rare. In experimental acute demyelinating disease, remyelination rapidly occurs owing to divisions of oligodendrocyte precursor cells (OPCs) and recapitulation of myelination program in the maturing oligodendrocytes. On the contrary, in chronic models of EAE, the proliferation and maturation processes of oligodendrocyte lineage cells are still scarcely known. In this study, we have described, by immunofluorescence confocal microscopy, and quantified, by morphometric analysis, immature and mature forms of the oligodendrocyte lineage in a mouse chronic model of myelin oligodendrocyte glycoprotein (MOG<sub>35-55</sub>) induced EAE. The study was performed at two different stages of EAE, early disease (20 dpi, days post-injection) and late disease (39 dpi). The results have demonstrated a severe cerebral cortex demyelination and a reactive increase of A2B5+ glial progenitor cells (GRPs) and NG2+/O4- OPCs during early EAE. GRPs and OPCs fell down in the EAE late phase, together with NG2+/O4+ pre-oligodendrocytes and CNPase+ mature oligodendrocytes. A compensatory differentiation attempt of proliferating precursors is suggested by the stable number of NG2-/O4+ pre-myelinating oligodendrocytes observed in 39 dpi EAE, but these cells appear to fail the last step of their differentiation, and signs of remyelination were absent in both early and late EAE. Overall, the results demonstrate that this chronic EAE model reproduces the features of primary progressive MS and that, despite the initial proliferative response of the oligodendroglial cells, exhausted cell division of oligodendrocyte progenitors and failure in oligodendrocyte differentiation impair the process of remyelination.

Key words

Remyelination failure