Mechanisms of myelin phagocytosis in multiple sclerosis

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Research question and background

Multiple sclerosis (MS) is characterized by phagocyte infiltration and myelin phagocytosis. Previous research has shown that besides complement and Fc receptors, scavenger receptors (SRs) might also contribute to demyelination. The aim of this research is to study the role of scavenger receptors in myelin phagocytosis in MS.

Methods and tissues used

Subregions (rim and perilesional normal-appearing white matter (PL-NAWM)) of chronic active and inactive MS lesions were isolated with laser dissection microscopy (LDM). Tissue from donors without neurological abnormalities was used as control tissue. The expression of selected SRs was quantified in this LDM and control tissue by qPCR. Furthermore, microarray analysis was performed to find novel genes involved in MS pathology. Genes of interest were stained in sections containing MS lesions or control tissue.

An *in vitro* phagocytosis assay was set up to study the functional role of SRs in myelin phagocytosis. Myelin was isolated from brain tissue of MS and control donors and labeled with the pH-sensitive dye pHrodo. Myelin phagocytosis was studied in the human monocytic cell line THP-1 or in primary human microglia isolated from human brain tissue of donors with different neurological background.

Results and conclusion

We have shown that SRs are selectively upregulated in and around chronic active MS lesions. SR-AI/II, CXCL16 and CD68 were expressed by foamy macrophages in the rim and by ramified phagocytes surrounding chronic active MS lesions, indicating their involvement in (early) demyelination. Microarray analysis has also revealed these and more interesting targets involved in MS pathology, including LOX-1. Blocking SR-AI/II or CXCL16 in our phagocytosis assays indeed downregulated myelin uptake, indicating their functional involvement in myelin phagocytosis. Functional studies blocking CD68 and LOX-1are now underway.

Furthermore, we hypothesized that the changes found in MS myelin in previous research could have functional consequences for its uptake. We therefore compared the uptake of myelin isolated from PL-NAWM of MS donors and control donors and indeed found that MS myelin is taken up more efficiently than control myelin by both THP-1 cells and primary human microglia. This indicates that factors in MS myelin might trigger demyelination.