

Mechanisms of myelin phagocytosis

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Research question and background

The aim of the project was to identify mechanisms involved in myelin phagocytosis. Previous research has shown that Fc receptors and the complement system are involved in myelin phagocytosis, but are not exclusively responsible for this uptake. Lately, scavenger receptors (SRs) have gained more interest as possible contributors to myelin phagocytosis. The main aim of this project was to identify new scavenger receptors that play a role in myelin phagocytosis, possibly in conjunction with the already known receptors.

Methodes and tissues used

We analysed of expression of scavenger receptors in and around MS lesions using Q-PCR and immunohistochemical techniques, studied efficacy of uptake of myelin from controls or MS NAWM by macrophages and primary human microglia and the involvement of different SRs that were found upregulated around expanding MS lesions in the uptake of human myelin by macrophages and human microglia. We investigated in gene expression study just outside the rim of chronic expanding MS lesions and inactive MS lesions aiming to identify molecules involved in initial events of demyelination or involved in the halt of demyelination, respectively and analysed macrophage phenotype in and around MS lesions using CD68, CR3 and IBA1 as markers.

Results and conclusion

Results show that the expression of several key SRs is increased around chronic active MS lesions and in nodules (reactive MS lesions) in normal appearing white matter: CD68, chemokine (C-X-C motif) ligand 16 (CXCL16), class A macrophage SR (SR-AI/II), LOX-1 (lectin-like oxidized low-density lipoprotein receptor 1), FcγRIII and LRP-1 (low-density lipoprotein receptor-related protein 1). Subsequent functional *in vitro* studies using locked RNAs, show functional implication of especially SR-AI/II and to a lesser extend of CXCL16 and CD68 in myelin uptake. In addition to increased expression of SRs around expanding MS lesions, also myelin isolated from MS brain donors from normal appearing white matter (NAWM) without signs of actual demyelination was taken up more efficiently by macrophages and primary human microglia. This shows that myelin of MS patients is already altered before demyelination. We found that HLA, Iba1 and CD68 identify different subtypes of microglia. These results warrant the use of microglia markers selected on the research question and neurological pathology to be studied. Genome wide transcriptional profiling of peri-lesional regions and rims of chronic active and inactive MS lesions identified, next to several SRs, some very interesting targets, such as CCL18, chitinase 1, CXCR4, granulin, NCAN and RUNX3 expressed in relation to MS lesion expansion and demyelination for future studies.