Liver X receptor activation in MS lesions.

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Research question and background

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS). It is pathologically characterized by infiltrating macrophages that destroy the myelin sheaths. Myelin consists for a large part of cholesterol and myelin breakdown causes an overload of cholesterol and oxysterols in macrophages. These oxidized derivatives of cholesterol are able to activate liver X receptors (LXRs), which will lead to the subsequent induction of genes involved in cholesterol efflux, including *ABCA1, ABCG1* and *APOE*. Previously, we demonstrated that myelin activates LXRs in primary murine macrophages.

Methods and tissues used

In this study we used real-time quantitative PCR (qPCR) and immunohistochemistry (IHC) to determine the expression of LXRs and their response genes in human phagocytes after myelin phagocytosis and in MS lesions.

Results and conclusion

Myelin ingestion induced the LXR response genes *ABCA1* and *ABCG1* in human monocyte derived macrophages, demonstrating myelin activates LXRs in human phagocytes. We found that both *ABCA1* and *APOE* gene expression and protein levels are highly upregulated in active MS lesions compared to healthy controls. MHCII-positive infiltrating macrophages and microglia in active lesions are positive for ABCA1 and APOE, indicating LXRs are activated in these myelin phagocytosing cells. LXRα is mainly present on MHCII+ cells while LXRβ is predominantly observed in perilesional astrocytes. Our findings indicate that LXRs are activated in phagocytes and perilesional astrocytes in active MS lesions. Future studies are needed to determine the impact of LXR activation on infiltrating and residential CNS cell types.