Liver X receptor activation in MS lesions.

Hasselt University, Biomedical Research Institute, School of Life Sciences, Diepenbeek, Belgium.
Division of Pharmacology, Vascular and Metabolic Diseases, Department of Internal Medicine, Rotterdam University, The Netherlands.
VU medical center, Molecular Cell Biology and Immunology, Amsterdam, The Netherlands.

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.