

Neurobiology



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Molecular Mechanisms of Myelin Formation and Maintenance in Health and Disease

Chronic Cortical Pathology in Multiple Sclerosis

Multiple sclerosis (MS) is the most common chronic inflammatory disease of the central nervous system and leads to long-term disability already in young adults. Its etiology is still unclear, but the interpretation of recent genome-wide association studies in MS, which identified almost exclusively immune system-related genes, has been that MS develops from the outside, i.e. the peripheral immune system, which then attacks the central nervous system. In the search of identifying factors preceding demyelination, we investigated the molecular pathomechanisms in the so-called normal appearing cortical grey matter, where there is no sign of inflammation and demyelination. We performed the to-date largest whole-genome gene expression study conducted with normal-appearing human brain cortical grey matter tissue of multiple sclerosis cases (Fig. 1). There we detected an upregulation of HLA-DRB1 gene expression in multiple sclerosis brain tissue compared to control cases. We were further able to link the high HLA-DRB1 gene expression to a higher frequency of HLA-DRB1*15:01 allele carriers amongst the multiple sclerosis cases. The HLA-DRB1*15:01 allele is known to be the strongest risk factor for developing multiple sclerosis. We were further able to link the elevated HLA-DRB1 gene expression to higher protein expression, mainly by brain-resident microglia cells, and notably to increased size of cortical grey matter lesions. The fact that HLA-DRB1*15:01 is expressed at higher levels in the brain parenchyma challenges the outside-in hypothesis of multiple sclerosis and demonstrates the possibility of relevant immunological mechanisms taking place within the brain itself, i.e. from the inside (Enz *et al.*, 2020).

Combinatory multifactor treatment effects on primary nanofiber oligodendrocyte cultures

Multiple sclerosis (MS) is a chronic inflammatory demyelinating and neurodegenerative disease of the central nervous system. Neurological deficits are attributed to inflammatory demyelination, which compromises axonal function and survival. These are mitigated in experimental models by rapid and often complete remyelination of affected axons, but in MS this endogenous repair mechanism frequently fails, leaving axons increasingly vulnerable to the detrimental effects of inflammatory and metabolic stress. Understanding the molecular basis of remyelination and remyelination failure is essential to develop improved therapies for this devastating disease. However, recent studies suggest that this is not due to a single dominant mechanism, but rather represents the biological outcome of multiple changes in the lesion microenvironment that combine to disrupt oligodendrocyte differentiation. This identifies a pressing need to develop technical platforms to investigate combinatory and/or synergistic effects of factors differentially expressed in MS lesions on oligodendrocyte proliferation and differentiation. We developed a protocol using primary oligodendrocyte cultures from B16 mice on 384-well nanofiber plates to model changes affecting oligodendrogenesis and differentiation in the complex signaling environment associated with multiple sclerosis lesions (Fig. 2). Using platelet-derived growth factor (PDGF-AA), fibroblast growth factor 2 (FGF2), bone morphogenetic protein 2 (BMP2) and bone morphogenetic protein 4 (BMP4) as representative targets, we demonstrate that we can assess their combinatory effects across a wide range of concentrations in a single experiment. This *in vitro* model is ideal for assessing the combinatory effects of changes in availability of multiple factors, thus more closely modelling the situation *in vivo* and furthering high-throughput screening possibilities (Enz *et al.*, 2019).

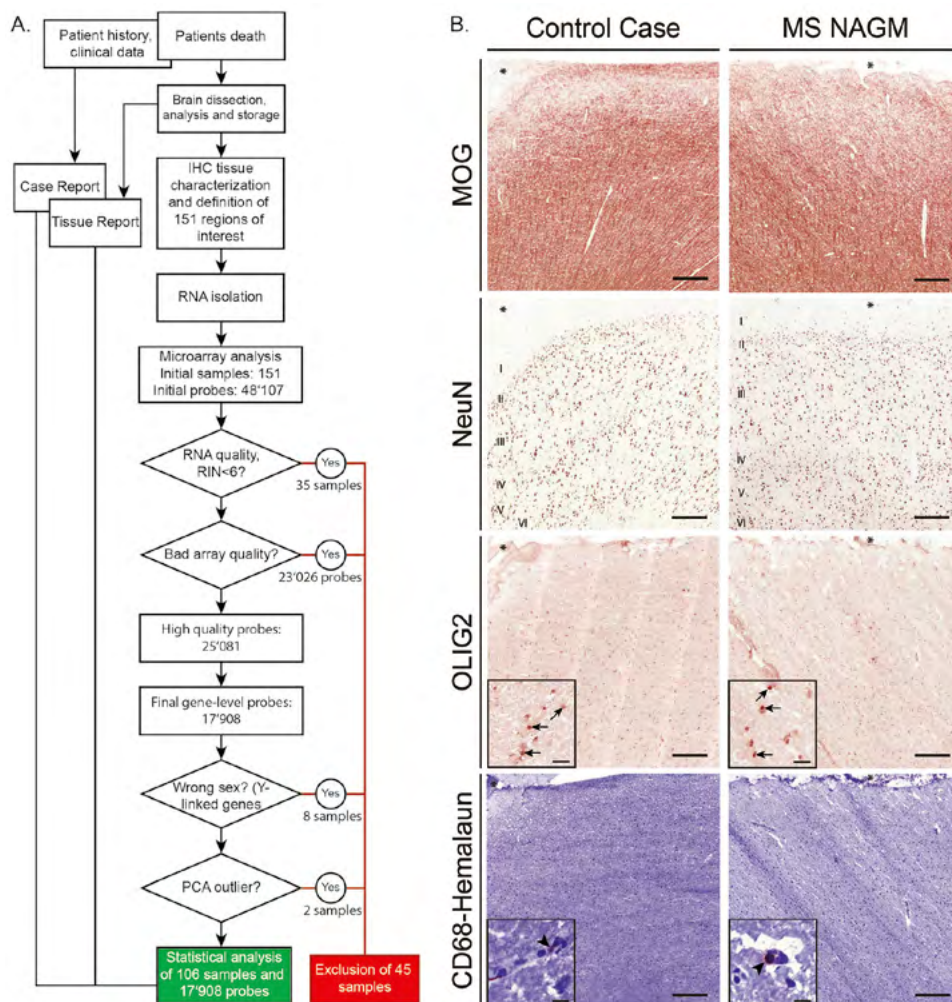


Fig. 1: Tissue processing for microarray and tissue characterization

(A) Flowchart to illustrate the process from the patient's death to statistical analysis of the gene expression microarray. After dissection of the brain and exclusion of confounding pathologies, the tissue blocks were sent from the UK MS Tissue Bank to Basel, Switzerland. There, an immunohistochemical characterization was performed, any tissue with bad preservation was excluded, and regions of interest were selected. After RNA isolation, the RIN was measured, and samples with RIN smaller than 6 were excluded. Sample mix up was checked by wrong sex and by principal component analysis. (B) Representative images of control cortical gray matter (case C30) and

MS NAGM (case MS08, asterisk delineates the meninges, I–VI indicate the 6 neuronal layers). NAGM was defined as no loss of MOG, NeuN, or OLIG2 (inset, arrows) staining compared with control cases and no increase in CD68 compared with controls; i.e., occasional CD68+ staining intra- or perivascular (inset, arrowheads) and nearly no CD68+ staining in the tissue. Scale bars: 250 µm; inset Olig2: 20 µm, inset CD68: 10 µm. IHC=immunohistochemistry; MOG=myelin oligodendrocyte glycoprotein; NAGM=normal-appearing cortical gray matter; NeuN=neuronal nuclei; OLIG2=oligodendrocyte transcription factor 2; PCA=principal component analysis; RIN=RNA integrity index. Image was copied from Enz *et al.*, 2020.

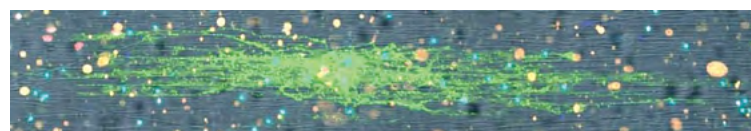


Fig. 2: MOG positive oligodendrocyte enwrapping nanofibers

Oligodendrocytes were cultured on nanofiber plates with 20ng/ml PDGF and 20ng/ml FGF2 for 3 weeks.

Selected Publications

Jäckle K, Zeis T, Schaeren-Wiemers N, Juncker A, van der Meer F, Kramann N, Stadelmann C, Brück W. Molecular signature of slowly expanding lesions in progressive multiple sclerosis. *Brain*. 2020 Jun 24;awaa158. doi: 10.1093/brain/awaa158. Epub ahead of print. PMID: 32577755.

Enz LS, Zeis T, Schmid D, Geier F, van der Meer F, Steiner G, Certa U, Binder TMC, Stadelmann C, Martin R, Schaeren-Wiemers N. Increased HLA-DR expression and cortical demyelination in MS links with HLA-DR15. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(2).

Enz LS, Zeis T, Hauck A, Linington C, Schaeren-Wiemers N. Combinatory Multifactor Treatment Effects on Primary Nanofiber Oligodendrocyte Cultures. *Cells*. 2019;8(11).

Zeis T, Howell OW, Reynolds R, Schaeren-Wiemers N. Molecular pathology of Multiple Sclerosis lesions reveals a heterogeneous expression pattern of genes involved in oligodendroglioneogenesis. *Exp Neurol*. 2018;305:76–88.

Zeis T, Enz L, Schaeren-Wiemers N. The immunomodulatory oligodendrocyte. *Brain Res*. 2016;1641(Pt A):139–48.