Remyelination impairment and HERV-W in Multiple Sclerosis

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The human endogenous retrovirus type W (HERV-W) was shown to participate in autoimmunity and to contribute significantly to brain damage as it is observed in Multiple Sclerosis (MS). We investigate endogenous repair mechanisms and to what extent they can be explored for myelin repair therapies. In this context differentiation of oligodendroglial precursor cells has been recognized as crucial for central nervous system remyelination and was furthermore shown to be influenced by various extrinsic and intrinsic factors. We addressed the question whether the HERV-W envelope protein (ENV) affects oligodendroglial differentiation and could thus influence remyelination related cellular processes. We found that the ENV protein is present in close proximity to TLR4-expressing oligodendroglial precursor cells adjacent to MS lesions. Human and rat oligodendroglial precursor cells expressed TLR4, and the ENV-mediated activation of TLR4 led to the induction of proinflammatory cytokines and inducible nitric oxide synthase as well as the formation of nitrotyrosine groups and a subsequent reduction in myelin protein expression. Neutralization of ENV by GNbAC1 was then found to reduce ENV‘s ability to induce stress and could rescue oligodendroglial myelin expression. This led to the conclusion that ENV-mediated nitrosative stress induction results in an overall reduction of the oligodendroglial differentiation capacity, thereby contributing to remyelination failure. However, beyond immune cell modulation, the monoclonal GNbAC1 antibody could also help to overcome the oligodendroglial differentiation blockade and to promote myelin repair in the diseased central nervous system.