Immunologically relevant genes are as well expressed by glia cells: a strong support of the hypothesis that multiple sclerosis is a primary degenerative disorder

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Introduction: Numerous studies report that the pathogenesis of multiple sclerosis (MS) is mediated by autoimmune inflammation, which results in oligodendrocytes degeneration, demyelination, gliosis and axonal damage. In line with this, genome-wide association studies (GWAS) show an overrepresentation of immunologically relevant genes. Other studies, however, have proposed that brain intrinsic degeneration is the initial factor driving lesion formation. Thus, it is tempting to speculate that immunologically relevant genes are expressed not only by immune cells but also by brain cells, which might contribute to immune cell recruitment and thus lesion formation.

Methods: Intrinsic degeneration was induced by intoxicating C57BL/6 with cuprizone. Tissues were analyzed by Affymetrix microarray analysis and immunohistochemical staining against CD44. The liaison of intrinsic degeneration and autoimmunity was realized by combining the cuprizone model with active EAE (i.e., Cup/EAE). Co-localization of CD44-positive cells with glial-cell markers (IBA1, Vimentin) and immune cell markers (CD4, CD3) was performed by immunofluorescence double stainings. $CX3CR1^{+/eGFP}$ $CCR2^{+/RFP}$ transgenic mice were used to distinguish between microglia and monocytes.

Results: Intrinsic degeneration induces the immunologically relevant gene *CD44*. CD44 was strongly induced at abluminal sites. The observed staining pattern suggested either expression of CD44 at the most distal astrocyte processes and/or secreted soluble CD44 in the extracellular space. To test the interaction between intrinsic degeneration and autoimmunity on CD44 expression, both models were combined. There, CD44 was expressed at the luminal and abluminal site. Detailed phenotypic characterization revealed that CD44 is expressed by both, brain cells (i.e., $Vimentin^+$ astrocytes, $eGFP^+$ microglia and RFP^+ monocytes) and infiltrating $CD3^+/CD4^+$ lymphocytes.

Conclusion: This study demonstrates that a classical immunologically relevant gene (CD44) is expressed by brain and immune cells in a MS relevant model. Expression of immunologically relevant genes, such as CD44 by glia cells might explain their overrepresentation in GWAS and might regulate MS lesion formation.