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P52

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 have shown that the pathogenesis of multiple sclerosis (MS) is mediated by autoimmune inflammation, which results in oligodendrocyte degeneration, demyelination, gliosis and axonal damage. In line with this, genome-wide association studies (GWAS) in MS patients 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. Their expression might contribute to immune cell recruitment and thus lesion formation.

Results

Cuprizone-induced metabolic injury mirrors pathology of early MS lesions

cuprizone

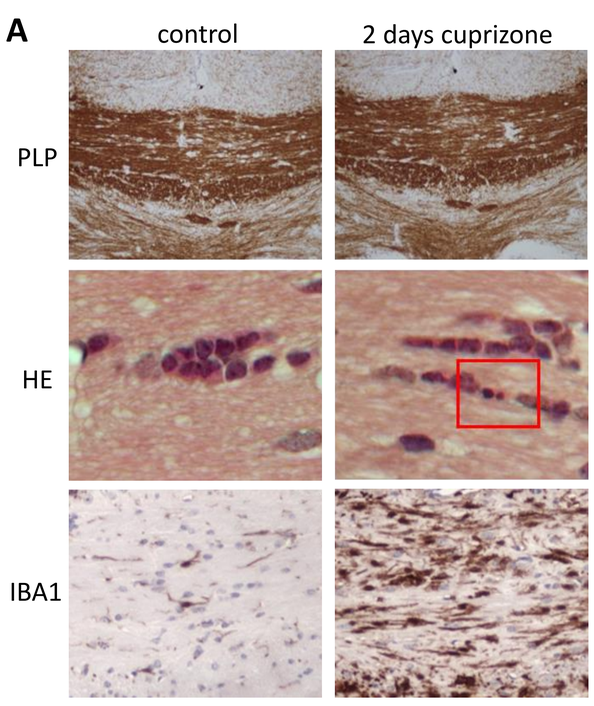

Figure 1 Histopathological characteristics of the cuprizone model. (A) Early cuprizone lesions (i.e., 2 days after initiation of the cuprizone intoxication) show minor myelin alterations (demonstrated by anti-PLP stain), oligodendrocyte apoptosis (shown by HE stain) and activation of microglia cells (shown by anti-IBA1 stain) in the midline of the corpus callosum (mCC). (B) The arrow indicates the mCC.

Intrinsic degeneration induces the expression of immunologically relevant genes

cuprizone

A

Gene symbol	1 week control	1 week cuprizone	fold change
Vcam1	8.83	9.37	0.55
Plek	8.68	9.39	0.70
Cd86	6.31	6.68	0.37
Myc	8.18	9.92	1.75
Pvt1	9.15	9.75	0.61
Tnfrsf1a	8.27	9.41	1.14
Stat3	10.01	11.22	1.21
Mettl1	8.47	9.02	0.54
Cd44	8.82	10.75	2.53

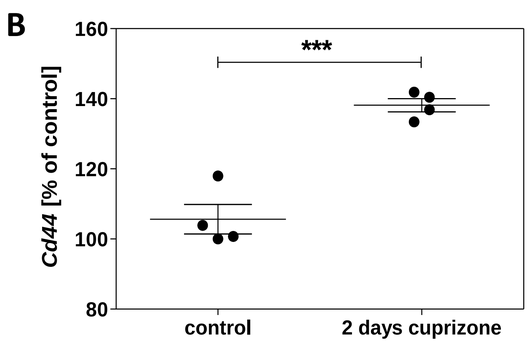

Figure 2 Gene transcription of immunologically relevant genes in cuprizone-treated mice. (A) Evaluation of Affymetrix GeneChip arrays shows that several immunologically relevant genes are upregulated in the corpus callosum after 1 week cuprizone intoxication. (B) Early *Cd44* mRNA induction during cuprizone intoxication ($p \leq 0.001$).

CD44 expression during cuprizone-induced demyelination

cuprizone

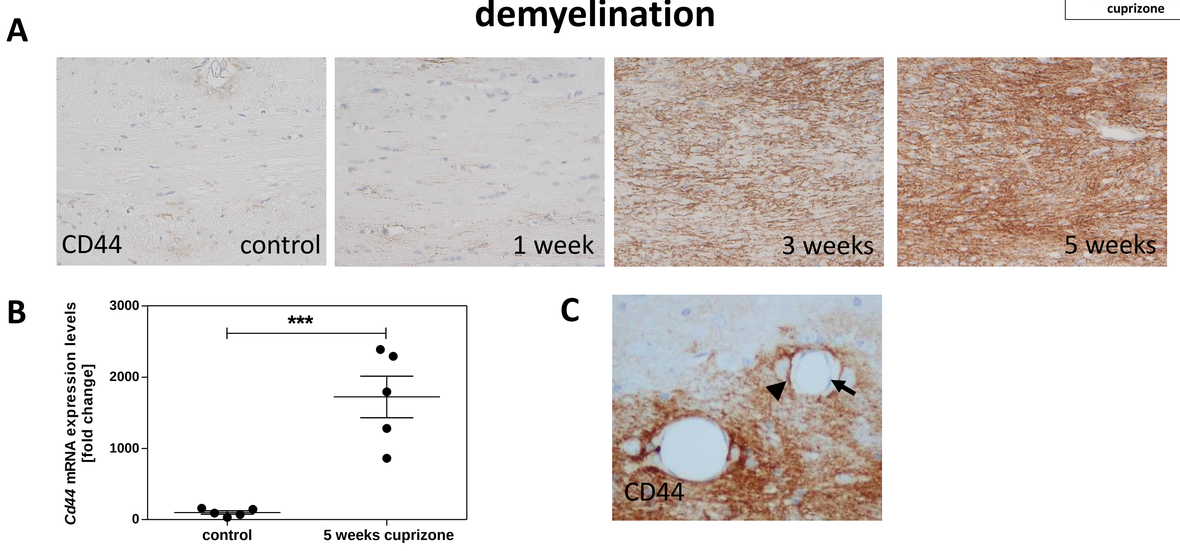

Figure 3 Protein and mRNA expression of CD44 in cuprizone-treated mice. (A) CD44 expression correlates with treatment duration and peaks at the time of complete demyelination (5 weeks). (B) mRNA expression levels of *Cd44* after 5 weeks cuprizone treatment. (C) CD44 is strongly induced at abluminal sites, but not by endothelial cells. Arrowhead marks the abluminal *glia limitans perivascularis*; arrow marks the endothelium.

Intrinsic degeneration triggers immune-cell recruitment

Cup/EAE

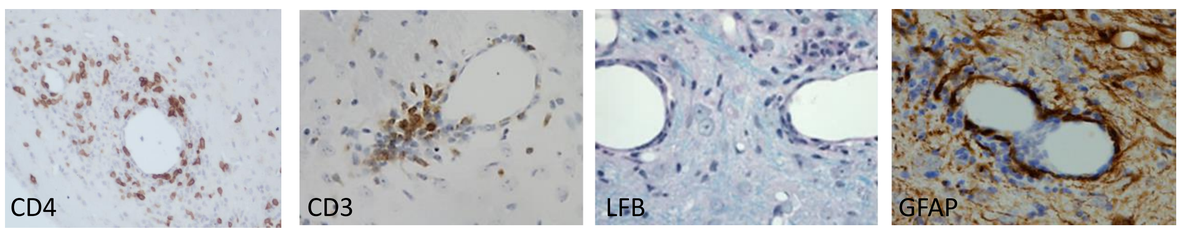

Figure 4 Histopathological characteristics of inflammatory forebrain lesions in Cup/EAE mice. Immune cell invasion (shown by anti-CD4 stain and anti-CD3 stain) induces focal demyelination (shown by LFB/PAS stain), which is paralleled by breakdown of the glia limitans perivascularis (shown by anti-GFAP stain (Rüther et al. 2017)).

Brain cells and peripheral immune cells express CD44

Cup/EAE

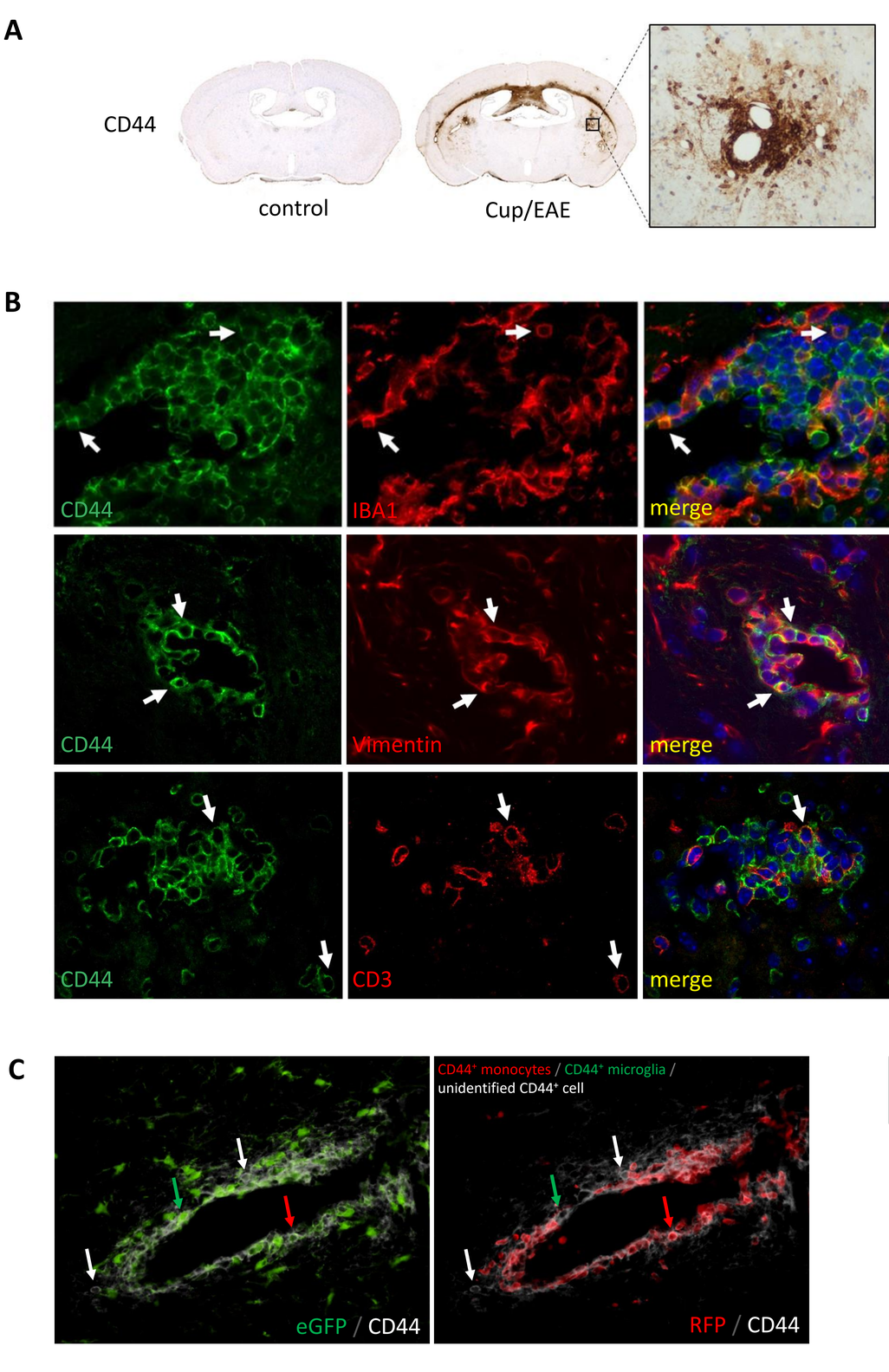

Figure 5 Immunofluorescence double stainings of CD44 and different glial/immune cell markers. (A) Perivascular infiltrates show a high CD44 immunoreactivity. CD44 is expressed at the luminal and abluminal site. (B) CD44 is expressed by brain cells (i.e., IBA1$^+$ cells) and peripheral immune cells (i.e., Vimentin$^+$ cells and CD3$^+$ cells). (C) Brain resident microglia and infiltrating monocytes express CD44.

Discussion

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

Literature

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