Identification of developmental endothelial locus-1 (Del-1) as a homeostatic factor in the central nervous system limiting multiple sclerosis

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Research question and background

The hallmark of neuroinflammatory demyelinating diseases in the central nervous system (CNS), such as multiple sclerosis (MS), is exacerbated inflammatory cell accumulation. Under normal conditions, the intact blood-brain barrier (BBB) prevents inflammatory cells from extravasating into the CNS. The BBB is thereby a component of the immune-privilege status of the CNS. In the course of MS and of its animal model, experimental autoimmune encephalomyelitis (EAE), the disruption of the BBB and the infiltration of autoreactive T cells and their respective cardinal cytokines, trigger a strong inflammatory response including the recruitment of further immune cells, such as neutrophils, monocytes/macrophages, and the activation of resident microglia, thereby leading to myelin damage. Regulation of leukocyte-endothelial interactions and immune cell recruitment represent an important therapeutic modality in EAE and MS. Whereas the majority of studies so far have focused on the activation of autoreactive and inflammatory cells in EAE and MS disease development, very little is known about alterations in homeostatic factors of the CNS that may counter-act MS/EAE pathogenesis. We have previously identified developmental endothelial locus-1 (Del-1) as an endogenous anti-inflammatory factor, which inhibits integrin-dependent leukocyte adhesion. Intriguingly, the highest expression of Del-1 has been observed in the CNS and Del-1 was implicated as a candidate MS susceptibility gene from a previous whole genome association study. We have thus hypothesized that Del-1 acts as an endogenous homeostatic CNS factor that contributes to the immune privilege status of the CNS.

Methods and tissues used

We therefore investigated the regulation of Del-1 expression in MS.
Real-time RT-PCR analysis was performed in human healthy control and MS brain tissues (frozen white matter tissues) that were provided by the Netherlands Brain Bank (NBB), Netherlands Institute for Neuroscience, Amsterdam, NL. All materials have been collected from donors from whom written informed consent for brain autopsy as well as for the use of the material and clinical information for research purposes without personal identification had been obtained by the NBB.

Results and conclusion

Quantitative PCR analysis demonstrated that Del-1 mRNA was downregulated in chronic active MS lesions, whereas Del-1 expression in chronic-inactive MS lesions was not significantly changed, as compared to samples from healthy control brain. Together with the results obtained using Del-1 deficient mice, we conclude that Del-1 is an endogenous homeostatic factor in the CNS protecting from neuroinflammation and demyelination.