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DISEASE MECHANISMS IN MS

Cell adhesion molecule MCAM on pathogenic T cells—a green light for CNS entry in multiple sclerosis

Melanoma cell adhesion molecule (MCAM) is expressed by a subset of inflammatory T cells and endothelial cells, and facilitates T-cell entry into the CNS during multiple sclerosis (MS), according to a recent study. Consequently, MCAM could be a promising biomarker and therapeutic target for MS.

> "...MCAM blockade restricts T_H17-cell migration through the blood–brain barrier"

In a proteomic analysis, Alexandre Prat, Catherine Larochelle and colleagues had previously identified expression of MCAM on human T-helper-17 (T_H17) lymphocytes—the effector T cells that enter the CNS and drive pathology in MS. "Other studies reported that MCAM supports melanoma cell invasion and metastasis, suggesting that this molecule plays a role in cell migration," says Larochelle, lead author of the current study. "We hypothesized that MCAM is involved in blood–brain barrier/T_H17-cell interaction and CNS infiltration by aggressive T lymphocytes."

Using *ex vivo*, *in vitro* and *in situ* approaches in human blood, cerebrospinal fluid (CSF) and CNS material, the investigators found MCAM is expressed on brain endothelial cells and on T_H17 cells. MCAM expression was upregulated in both cell types in MS lesions, with the highest proportion of MCAM-expressing $CD4^+$ lymphocytes observed in the blood and CSF during MS relapse. Furthermore, administration of an MCAM-blocking antibody to mice with MS-like disease reduced disease severity.

"We confirmed that MCAM participates in adhesion of T_H17 cells to the endothelium," says Larochelle. "Most importantly, we demonstrate that MCAM expression identifies $CD4^+$ T cells with encephalitogenic potential, and that MCAM blockade restricts T_H17-cell migration through the blood–brain barrier."

Given that upregulation of MCAM has been observed in patients with inflammatory disorders such as arthritis, the authors propose a crucial role for MCAM in organ-targeted inflammatory processes. The researchers now aim to assess the utility of MCAM as a biomarker for MS, and to determine the therapeutic potential of anti-MCAM antibodies in patients with MS.

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Original article Larochelle, C. *et al.* Melanoma cell adhesion molecule identifies encephalitogenic T lymphocytes and promotes their recruitment to the central nervous system. *Brain* doi:10.1093/brain/aws212