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Integrin alpha8 is a novel mediator of T lymphocyte migration across the CNS barriers

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Background and Objectives: Active migration of proinflammatory T lymphocytes from the peripheral blood (PB) across the central nervous system (CNS) barriers is a critical part of multiple sclerosis (MS) pathogenesis. These barriers include the tightly regulated blood-brain barrier (BBB) and the blood-meningeal barrier (BMB). Integrins, which are heterodimeric alpha/beta transmembrane proteins, facilitate leucocyte transmigration by mediating cell-cell or cell-extracellular matrix protein interactions. Beta1 integrin heterodimers have been associated with the migration of PB lymphocytes across CNS barriers, as supported by the strong clinical efficacy of Natalizumab, a monoclonal antibody targeting integrin alpha4beta1. However, due to widespread expression of alpha4beta1 across leucocyte subsets, Natalizumab treatment is associated with impaired immune surveillance and susceptibility to severe viral infections. Therefore, our goal is to identify novel beta1 integrin partners involved in the specific migration of pathogenic T lymphocytes across the CNS vasculature in order to solve this unmet clinical need.

Methods and Results: Whole cell lysate proteomic analysis reveals that proinflammatory TH17 cells express integrin alpha8, which heterodimerizes exclusively with integrin beta1. Here we show through qPCR, western blot and immunocytochemistry that alpha8 is specifically expressed by activated CD4+ and CD8+ T lymphocytes and is upregulated in pro-inflammatory conditions in healthy controls and MS patients. Immunofluorescence reveals that alpha8 is expressed on CD3+ T cell infiltrates in MS and mouse experimental autoimmune encephalomyelitis (EAE) brains. Furthermore, we demonstrate via RT-PCR, western blot and immunofluorescence that both BBB and BMB endothelial cells (ECs) express the main ligand of alpha8, nephronectin (NPNT). Blockade of the alpha8 binding site decreases TH1 and TH17 cell migration across a monolayer of BBB-ECs in vitro. Moreover, therapeutic i.p. injections of alpha8 blocking peptide, as compared to control peptide, reduces clinical severity, limits T lymphocyte infiltration into the CNS and prevents disease progression in MOG35-55 - induced EAE mice.

Conclusions: These data highlight an important role for alpha8 in mediating pro-inflammatory T lymphocyte migration across the CNS microvasculature, suggesting that this integrin may be an effective therapeutic target to prevent disease activity and progression in MS.

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