?4-integrins control viral meningoencephalitis through differential recruitment of T helper cell subsets.

Abstract:
Natalizumab blocks ?4-integrins and is a prototypic agent for a series of anti-inflammatory drugs that impair trafficking of immune cells into the CNS. However, modulation of the access of immune cells to the CNS is associated with impaired immune surveillance and detrimental viral infections of the CNS. Here, we explored the potency of cellular immune responses within the CNS to protect against viral encephalitis in mice with T cell conditional disruption of VLA-4 integrin (?4?1) expression. While VLA-4 expression in virus specific Th1 cells is non-redundant for their ability to access the CNS, ?4-integrin deficient Th17 cells enter the CNS compartment and generate an inflammatory milieu upon intrathecal vaccinia virus (VV) infection. However, in contrast to Th1 cells that can adopt direct cytotoxic properties, Th17 cells fail to clear the virus due to insufficient Eomes induced perforin-1 expression. The quality of the intrathecal cellular antiviral response under conditions of impaired VLA-4 function jeopardizes host protection. Our functional in vivo data extend our mechanistic understanding of anti-viral immunity in the CNS and help to estimate the risk potential of upcoming therapeutic agents that target the trafficking of immune cells into distinct...
anatomical compartments.

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