NEUROIMMUNOLOGY

Basement membrane laminins guard the CNS

The extravasation of myelin-specific $CD4^+$ T cells from the blood into the central nervous system (CNS) is a crucial factor in the pathogenesis of multiple sclerosis. We know much about how leukocytes traverse the endothelial cell monolayer of post-capillary venules, but far less is known about how they cross the underlying basement membrane, which is the rate-limiting step in transmigration. Recent research indicates a role for basement membrane laminins in specifically regulating the migration of $CD4^+$ T cells into the CNS, which could lead to more specific therapies for multiple sclerosis.

Endothelial basement membranes are characterized by laminin 411 (composed of α4, β1 and γ1 chains) and laminin 511 (composed of α5, β1 and γ1 chains), with uniform distribution of laminin α4 but patchy distribution of laminin α5. Leukocyte extravasation preferentially occurs at laminin $\alpha4^{hi}$ laminin $\alpha5^{low}$ sites; to investigate the role of basement membrane laminins in regulating this process, the authors studied laminin α4-deficient (*Lama4*$^{-/-}$) mice with experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis.

Lama4$^{-/-}$ mice have compensatory ubiquitous expression of laminin α5 along all blood vessels but otherwise have normal expression of adhesion molecules and junctional proteins. After immunization with myelin oligodendrocyte glycoprotein (MOG), *Lama4*$^{-/-}$ mice had decreased EAE susceptibility and severity, which correlated with decreased numbers of $CD4^+$ T cells in the CNS. *Lama4*$^{-/-}$ mice that received wild-type bone marrow also had decreased EAE incidence and severity after MOG immunization, which excludes an immune cell defect. Indeed, *Lama4*$^{-/-}$ mice had normal infiltration of leukocytes into peripheral tissues and normal levels of T cell proliferation. A specific defect in the migration of T cells across post-capillary venules in the CNS was confirmed by the transfer of wild-type encephalitogenic T cells to *Lama4*$^{-/-}$ or wild-type recipients. Three days after transfer (before T cell proliferation has begun), *Lama4*$^{-/-}$ mice had the same number of peripheral donor T cells but significantly lower numbers of donor T cells in the CNS compared with wild-type recipients, which resulted in decreased incidence and severity of EAE.

In *in vitro* transwell assays, T cells migrated extensively across laminin 411 but not across laminin 511. Antibodies specific for α6β1 integrin, which is the main receptor for laminin α4 expressed by T cells, inhibited transmigration across laminin 411, as did increasing levels of laminin 511 in a dose-dependent manner. These data indicate that laminin α5 inhibits α6β1 integrin-mediated T cell migration across laminin α4. α6 integrin-deficient (*Itga6*$^{-/-}$) bone marrow-chimeric mice had decreased EAE severity after MOG immunization, and a similar effect resulted from antibody-mediated blockade of α6 integrin.

As the α6β1 integrin-mediated migration across laminin α4 seems to preferentially occur for $CD4^+$ T cells and not $CD8^+$ T cells, macrophages or dendritic cells, targeting this interaction could provide a more specific therapeutic strategy for multiple sclerosis to inhibit $CD4^+$ T cell-mediated neurodestruction without compromising other immune responses.

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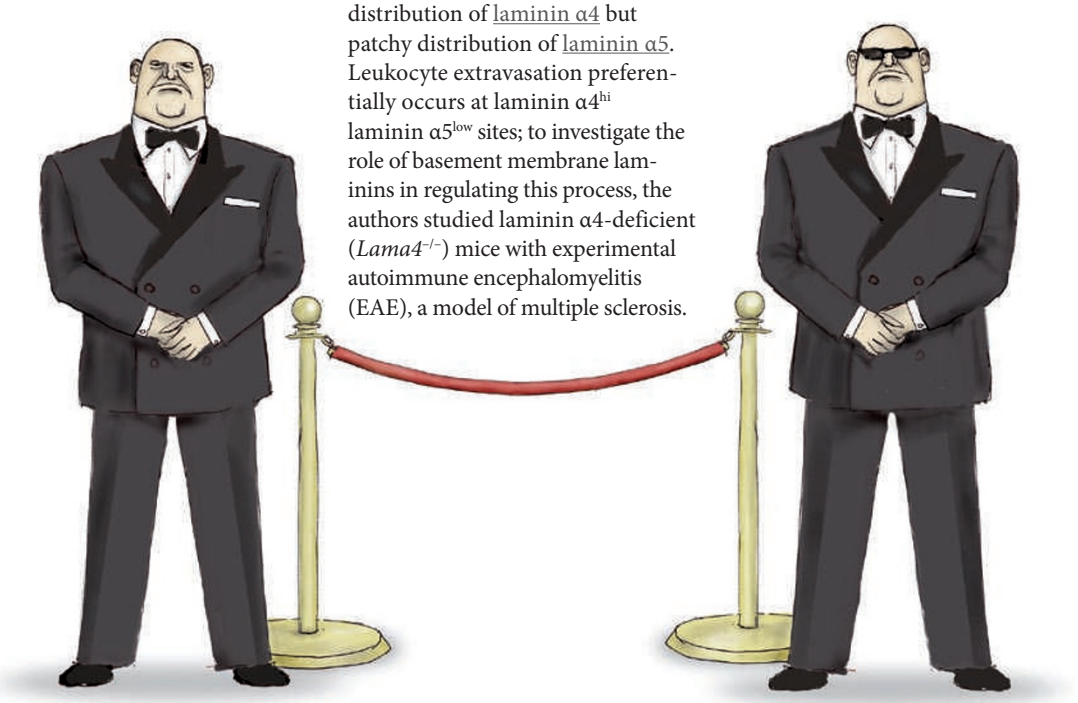

ORIGINAL RESEARCH PAPER Wu, C. *et al.* Endothelial basement membrane laminin α5 selectively inhibits T lymphocyte extravasation into the brain. *Nature Med.* **15**, 519–527 (2009)