MULTIPLE SCLEROSIS

Laminins control T-cell entry into the CNS

The mechanism by which T lymphocytes are able to penetrate the endothelial basement membrane barrier to gain entry to the CNS in multiple sclerosis (MS) could hold useful clues for developing novel therapeutic strategies. German researchers have shown that T lymphocytes migrate across the endothelial basement barrier at sites that are rich in laminin α4, but not at sites that contain predominantly laminin α5. "Laminin composition of the endothelial cell basement membrane has a selective effect on encephalitogenic T-lymphocyte extravasation into the CNS independently of basement membrane architecture," comments senior researcher Lydia Sorokin (Münster University, Germany).

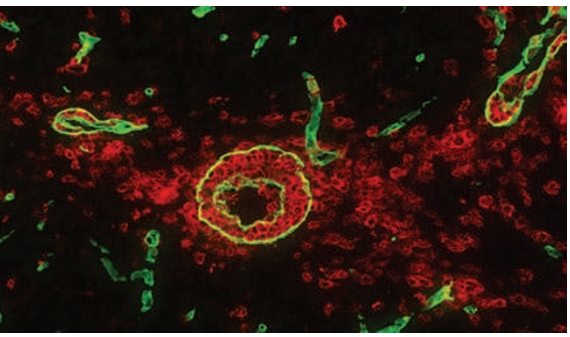

Figure 1 | Brain section showing laminin in the basement membranes (green). Infiltrating T cells appear in red. Image provided by Dr Lydia M. Sorokin.

A key experimental observation was made in the laminin α4 knockout mouse, which also shows ubiquitous laminin α5 expression in all endothelial cell basement membranes but otherwise expresses normal adhesion molecules and junctional proteins. "In a model where the endothelial basement membrane contains no laminin α4, T lymphocytes show significantly reduced migration into the CNS, suggesting that the laminins impart specific information to the T cell which controls migration," notes Sorokin. Macrophage and dendritic cell infiltration of the CNS was relatively unaffected. "This provides a rationale for specifically targeting T-lymphocyte infiltration into the CNS, particularly in autoimmune conditions such as MS," she adds.

The study suggests that targeting integrin-mediated interactions between T cells and laminin α4 in the endothelial cell basement membrane could allow very specific inhibition of T-lymphocyte entry into the CNS. Therapeutic agents used in MS at the moment, such as anti-integrin α4 or the anti-proinflammatory cytokines, dampen all immune responses. Selective inhibition of T-lymphocyte-associated events without compromising innate immune responses could theoretically be very beneficial. Sorokin cautions, however, that "it is not yet known whether the laminins play a role in other neuroinflammatory processes, and no current MS therapy is based on inhibiting T lymphocyte–laminin interactions; this is a long way from the clinic."

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