CD317 puts the brakes on dendritic cell trafficking to the CNS

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Myelin-reactive immune cell attack in multiple sclerosis (MS) causes inflammatory demyelinating lesions in the central nervous system (CNS), resulting in an array of neurological complications, which may result in permanent disability (1). The first episode of neurological symptoms is termed "clinically isolated syndrome" (CIS). Arresting disease pathogenesis during CIS is crucial to prevent progression to MS. Understanding the cellular and molecular mechanisms that favor conversion of CIS to MS is essential for timely prevention of CNS autoimmunity leading to neurodegeneration and permanent disability. In PNAS, Manouchehri et al. identify a dendritic cell subset that is crucial for initiating neuroinflammation and may be an important clinical target during conversion from CIS to clinically definite MS (2).

While many factors are hypothesized to participate in MS pathogenesis, it is well established that demyelination is driven by the activation and trafficking of autoreactive T cells into the CNS. Several effective treatments have been developed to prevent T cell trafficking into the CNS, including fingolimod and natalizumab (3). Fingolimod is a sphingosine-1-phosphate receptor modulator that sequesters T cells in lymph nodes. Natalizumab is a monoclonal antibody that targets the α4 chain of very late antigen-4 (VLA-4, also known as α4β1), which is an integrin that is necessary for leukocyte trafficking into the CNS.

Although MS was initially thought to be primarily driven by autoreactive T cells, advances in the field have revealed important roles for other leukocytes—especially those involved in antigen presentation and T cell priming. B cells have been shown to be important antigen-presenting cells and producers of proinflammatory cytokines (4). Depletion of B cells using rituximab, a monoclonal antibody targeting the CD20 antigen expressed by B cells, has shown efficacy in MS (5). However, there are no current therapies specifically targeting other antigen-presenting cells such as dendritic cells or monocyte-derived macrophages.

Because of the pathogenic effects of numerous immune cell types, efforts to prevent leukocyte infiltration in the CNS have become an important strategy in the development of MS therapeutics. The main approach for doing so has been to use antibodies that prevent interactions between integrins and adhesion molecules, which is essential for immune cell trafficking. A recent effort to impair leukocyte infiltration into the CNS targeted the ligand of VLA-4, vascular cell adhesion protein 1 (VCAM-1), which is expressed by vascular endothelial cells during neuroinflammation (6). Emerging evidence also suggests that natalizumab may work by targeting various immune subsets rather than T cells alone. Indeed, natalizumab treatment has been associated with decreased frequencies of dendritic cells in perivascular spaces within the CNS (7).

Dendritic cells, which are considered "professional" antigen presenters, play a key role in priming autoreactive T cells and maintaining their activation status during MS progression. Manouchehri et al. (2) therefore hypothesized that inhibiting dendritic cell migration to the CNS would protect against MS pathology. Using a mouse model of MS known as experimental autoimmune encephalomyelitis (EAE), they demonstrate that selective knockout of the α4 integrin in dendritic cells results in delayed EAE onset and significantly reduces frequencies of dendritic cells in primary and secondary lymphoid organs. They further determine that $CD11c^+$ dendritic cells lacking α4 integrin maintain their antigen presentation capacity and ability to induce T cell proliferation, suggesting that α4 integrin deletion works specifically by preventing dendritic cell migration rather than impairing dendritic cell effector functions. These findings suggest that impairment of dendritic cell migration may be an important mechanism by which natalizumab acts.

In addition to identifying an additional mechanism of action for natalizumab, Manouchehri et al. (2) also identify a dendritic cell subset that is essential for EAE pathology. By taking advantage of the delayed disease onset window in mice with dendritic cell-specific α4

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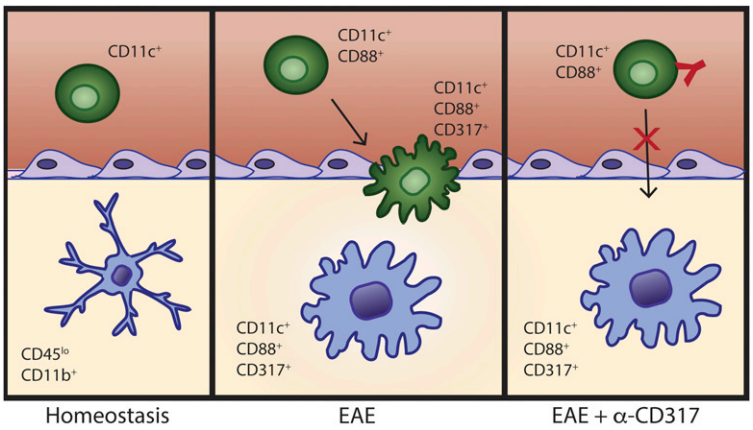

Fig. 1. CD317 blockade ameliorates EAE. Early in EAE pathology, a subset of circulating CD11c$^+$ cells up-regulates CD88. CD317 up-regulation on these cells is associated with trafficking to the perivascular spaces of the CNS. A similar subset of CD11c$^+$CD88$^+$CD317$^+$ microglia-like cells is observed in the cerebrospinal fluid of patients with MS. Treatment with a monoclonal antibody targeting CD317 reduces trafficking of CD11c$^+$ CD88$^+$ cells to the CNS and abrogates EAE pathology.

knockout, they observe the early appearance of CD11c$^+$CD88$^+$ cells in the blood, which further express CD317 upon entry into the CNS. CD317 (also known as tetherin, BST2, and PDCA-1) is a lipid raft-associated protein thought to be involved in cell adhesion and migration. As such, Manouchehri et al. (2) hypothesized that CD317 blockade would ameliorate EAE pathology by inhibiting the migration of CD11c$^+$CD88$^+$ cells into the perivascular spaces of the CNS. Indeed, they demonstrate that treatment with a monoclonal antibody targeting CD317 prior to EAE induction results in reduced frequencies of CD11c$^+$CD88$^+$CD317$^+$ cells in the brain and spinal cord and ameliorates acute EAE, with complete resolution of clinical disease (Fig. 1). Manouchehri et al. (2) therefore build upon previous efforts to inhibit leukocyte infiltration into the CNS by revealing CD317 as a potential therapeutic target.

Interestingly, CD317 has been shown to be expressed on a subset of dendritic cells known as plasmacytoid dendritic cells (pDCs), which produce large quantities of type I interferons and play an essential role in antiviral immune responses (8). It is hypothesized that the pathogenic effect of pDCs in the context of MS may be related to their role in antiviral immune responses preceding and contributing to MS onset. Previous studies have also implicated pDCs in MS pathology via interferon-alpha production, secretion of chemokines that attract autoreactive CD4$^+$ T cells, and up-regulation of the chemokine receptor CCR7, which directs pDCs to secondary lymphoid organs where they can prime T cells (9). Treatment with interferon-beta, another immunomodulatory drug used to treat MS patients, impaired each of these pathogenic functions of pDCs from patients with MS. Nonetheless, no attempt has been made to selectively deplete pDCs in the context of EAE or MS. While further studies are needed to confirm the subset identity and effector functions of CD11c$^+$CD88$^+$ CD317$^+$ dendritic cells in the context of EAE and MS, the use of a monoclonal antibody targeting CD317 may in fact prove to be the first attempt at a pDC-targeted therapy. Given the role of pDCs in other conditions such as rheumatoid arthritis, inflammatory bowel disease, and systemic lupus erythematosus (10), it will also be interesting to determine whether anti-CD317 treatment is efficacious in autoimmune conditions besides MS.

While Manouchehri et al. (2) demonstrate potential for CD317 blockade as a therapeutic target in the treatment of MS, further studies are required to determine the safety and efficacy of this drug. In this study, CD317 blockade is administered prior to EAE induction, much earlier than patients would present in the clinic. It will therefore be essential to determine the time point(s) at which anti-CD317 can be administered and still be effective in treating disease. Because of the apparent role of dendritic cells in the initiation of neuroinflammation, it may be crucial to administer anti-CD317 during CIS in order to prevent progression to MS. Furthermore, it would be valuable to identify cellular biomarkers to measure drug responsiveness and to predict progression or relapse. Findings from this study suggest that CD11c$^+$CD88$^+$ frequencies in the blood may be an important indicator of imminent relapse.

In addition to efficacy, the safety of CD317 blockade would need to be very closely examined. CD317 is expressed to varying degrees in most organs and can be expressed by many different cell types including hepatocytes, pneumocytes, ducts of major salivary glands, pancreas and kidney, Paneth cells, epithelia, Leydig cells, B cells, bone marrow stromal cells, monocytes, and vascular endothelium (11). Importantly, CD317 expression in many of these cells is crucial for organ-specific antiviral immunity, so prolonged use of CD317 blockade could put patients at risk for severe viral infections. Similarly, natalizumab treatment is associated with risk of opportunistic John Cunningham virus infection, which can result in serious and potentially fatal progressive multifocal leukoencephalopathy (12). Finally, it is essential to determine whether CD317 blockade selectively inhibits dendritic cell migration to the CNS or whether other peripheral organs are also affected. Outside of the CNS, dendritic cells play an essential role in maintaining immune tolerance to self-antigens and healthy microbiota (13). Breaking this tolerance could result in autoinflammation in other organs. Dendritic cells are also essential for immune surveillance and maintaining immunological memory (14). Impairment of dendritic cell migration to lymphoid organs could therefore interfere with immune responses to invading pathogens. Nonetheless, MS is a highly debilitating disorder, so careful consideration must be paid to the costs and benefits of any new therapy.

While autoreactive T cells play a dominant role in demyelination, innate immune cells—especially antigen-presenting cells like dendritic cells—are essential for T cell priming, activation, and proliferation. They are therefore critical in early pathogenesis and may be an important clinical target for preventing patient progression from CIS to MS. Throughout disease progression,

antigen-presenting cells maintain T cell activation and proliferation, so targeting them even at later disease stages may be beneficial. In their report in PNAS, Manouchehri et al. (2) not only identify a dendritic cell subset that is critical for early neuroinflammation during MS but also propose anti-CD317 as a therapeutic to target them.

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