Targeting brain infiltrating myeloid cells

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Neuroinflammation is driven by interactions between central nervous system (CNS) resident glial cells and infiltrating peripheral immune cells. In many neuroinflammatory disorders, like multiple sclerosis (MS), the incursion of myeloid cells significantly influences disease onset and progression. A key challenge in the neuroinflammation field is targeting the CNS-inflating cells. A major challenge in neuroinflammation research is the selective targeting of these CNS-infiltrating cells. Currently, monoclonal antibodies (mAbs) are available to reduce or prevent lymphocyte entry (e.g., natalizumab for T-cells, ocrelizumab for B-cells), but there are no equivalent therapies for CNS-infiltrating myeloid cells (CIMs). Distinguishing CIMs from resident macrophages (microglial cells) is difficult due to overlapping expression markers despite their distinct and sometimes contradictory roles in disease. Several unique microglial markers have been identified in the last decade, yet a clinically relevant marker for CIMs remains undiscovered. To address this gap in our understanding of CNS inflammation, we hypothesized that CD007, a novel surface receptor, distinguishes CIMs from resident microglial cells and thus potentially enables targeted therapy to mitigate neuroinflammation. To study this hypothesis, we focused on MS and its animal model, experimental autoimmune encephalomyelitis (EAE), in which CIMs play a prominent role. We have found that CD007 is not expressed in the healthy CNS of humans and mice and can only be detected during disease, where its expression is confined to CIMs. Next, we developed CD007-specific depleting-mAbs and found that *in-vivo* administration of mAbs reduced the presence of $CD007^{+}$ myeloid cells in the blood and impeded their recruitment to CNS. Resulting in halting disease progression in acute neuroinflammation and attenuating it in chronic/progressive EAE. Additionally, we created anti-CD007-IL10 (D265A) diabodies, which lack the cell-depleting functionality, but promote IL-10-dependent signaling. We found that *in-vivo* administration of these diabodies attenuates EAE progression. Our findings suggest that CD007 is a novel marker for blood-derived myeloid cells in the inflamed CNS and could represent a new avenue for disease-modifying therapies in MS and similar conditions.