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A novel immune role for NgR on b-cell populations localized in the central nervous system in a mouse model of multiple sclerosis

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Abstract

Despite clear evidence demonstrating that the deletion of Nogo-receptor 1 (NgR1) can protect against axonal degeneration and thus progression of experimental autoimmune encephalomyelitis (EAE), an immunological role for this receptor is yet to yield mechanistic evidence. However, recently NgR has been suggested as an alternate receptor for the B-cell activating factor (BAFF) in the central nervous system (CNS). Therefore, our strategic aim was to define whether NgR contributes within the modulation of the adaptive immune reaction during EAE by promoting maturation and differentiation of BAFF-reactive B-cells within follicles during the induction of disease. The results showed that CNS-infiltrating blood cells revealed an augmented response within the B-cells, which expressed NgR1 and NgR3, observed in ngr1+/+ mice with the onset and progression of the disease that would not be demonstrated within the spinal cords of EAE-induced ngr1-/- mice. Remarkably, a cluster of B-cells-expressing NgR was present at the meninges of lumbosacral spinal cords of the of ngr1+/+ EAE-induced mice at clinical score 1. Furthermore, there have been significant increases of secreted immunoglobulins from these NgR1-expressing B-cells. Importantly, these cells might be directed into the synthesis phase of the cell cycle, after stimulating sorted cells by extracellular BAFF in vitro; however, when BAFF signaling was blocked using either rBAFF-R, or NgR1-Fc, or NgR3 peptides, the cells were observed to be into G0/G1 phase. As a consequence, once we blocked NgR1-ligand signaling employing a novel hematopoietic stem cell-based delivery of a therapeutic protein, immune lineage-differentiated cells, including ZsGreen and fusion protein, were trafficking into the CNS during acute EAE. Collectively, these data indicate that the existence of an inducible expression of NgR1 and NgR3 in specific immune lineage cells upon the induction of EAE, which the follicular-like NgR1 and NgR3-positive B-cells within the meninges may play a lively role during the induction of EAE. Thus, our data reinforce the idea that blocking the interaction of BAFF and NgR1 and NgR3 may be vital for neuroprotection during inflammatory insults.

Clinical trial results of peripheral B cell depletion indicate abnormal proinflammatory B cell properties, and particularly antibody-independent functions, contribute to relapsing MS disease activity. However, potential roles of B cells in progressive sorts of disease still be debated. Prior work indicates that presence of B cells is fostered within the inflamed MS central nervous system (CNS) environment, and that B cell-rich immune cell collections may be present within the meninges of patients. A potential association is reported between such meningeal immune cell collections and therefore the subpial pattern of cortical injury that's now considered important in progressive disease. Elucidating the characteristics of B cells that populate the MS CNS, how they traffic into the CNS and the way they'll contribute to progressive sorts of the disease has become of considerable interest.

Here, we'll review characteristics of human B cells identified within distinct CNS sub compartments of patients with MS, including the spinal fluid , parenchymal lesions, and meninges, also as the relationship between B cell populations identified in these sub compartments and therefore the periphery. We will further describe the different barriers of the CNS and the possible mechanisms of migration of B cells across these barriers. Finally, we'll consider the range of human B cell responses (including potential for antibody production, cytokine secretion, and antigen presentation) which will contribute to propagating inflammation and injury cascades thought to underlie MS progression.

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