B cells, plasma cells, and antibodies are commonly found in active central nervous system (CNS) lesions in patients with multiple sclerosis (MS). B cells isolated from CNS lesions as well as from the cerebrospinal fluid (CSF) show signs of clonal expansion and hypermutation, suggesting their local activation. Plasma blasts and plasma cells maturing from these B cells were recently identified to contribute to the development of oligoclonal antibodies produced within the CSF, which remain a diagnostic hallmark finding in MS. Within the CNS, antibody deposition is associated with complement activation and demyelination, indicating antigen recognition-associated effector function. While some studies indeed implied a disease-intrinsic and possibly pathogenic role of antibodies directed against components of the myelin sheath, no unequivocal results on a decisive target antigen within the CNS persisted to date. The notion of a pathogenic role for antibodies in MS is nevertheless empirically supported by the clinical benefit of plasma exchange in patients with histologic signs of antibody deposition within the CNS. Further, such evidence derives from the animal model of MS, experimental autoimmune encephalomyelitis (EAE). In transgenic mice endogenously producing myelin-specific antibodies, EAE severity was substantially increased accompanied by enhanced CNS demyelination. Further, genetic engineering in mice adding T cells that recognize the same myelin antigen resulted in spontaneous EAE.
development, indicating that the coexistence of myelin-specific B cells, T cells, and antibodies was sufficient to trigger CNS autoimmune disease. In conclusion, various pathological, clinical, immunological, and experimental findings collectively indicate a pathogenic role of antibodies in MS, whereas several conceptual challenges, above all uncovering potential target antigens of the antibody response within the CNS, remain to be overcome.

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