Unraveling the T-B tangle in anti-CD20 multiple sclerosis therapy

Ari Waisman* and Anna Ebering*

Multiple sclerosis (MS) is an inflammatory T cell-mediated disease of the central nervous system (CNS) (1). It is characterized by focal demyelination and axonal loss leading to a range of symptoms including decline in motor function and sense perception (2). In PNAS, Sabatino et al. (3) further shed light on the underlying mechanism of current MS therapies. In mice, MS can be modeled by immunization with myelin-derived antigens, leading to a disease termed experimental autoimmune encephalomyelitis (EAE) (4). Many studies have defined the cells that are important in the activation of the T cells involved in EAE (5) as well as the role of the T cells involved in disease pathogenesis (6). In humans, neither a definite genetic nor environmental cause has been defined, nor has a cure been discovered for MS (7). Nevertheless, genetic studies have shown that genes of the immune system are highly associated with disease development (8). Importantly, one of the hallmarks of MS is the presence of oligoclonal immunoglobulin (Ig) bands in the cerebrospinal fluid (CSF) of patients, thus connecting disease activity to B cells, which are the origin of Ig-producing plasma cells (9). Nevertheless, a direct link between B cells themselves and disease pathogenicity has neither been shown in MS nor EAE, as the disease in mice is independent of these cells (10). Therefore, the findings that treatment with the monoclonal antibodies rituximab and ocrelizumab, directed against the B cell marker CD20, successfully led to a strong reduction in disease progression and activity were quite unexpected as MS was thought to be a T cell-mediated disease (1, 11). Importantly, although both rituximab and ocrelizumab target B cells, their effect on already established plasma cells is minimal, as these cells do not express CD20 (Fig. 1). Thus, B cells are depleted but plasma cells and along with them oligoclonal Ig bands are retained (12). These findings propose that B cells are directly involved in MS pathogenicity, in an unknown mechanism—but which? One possibility suggests that these cells can function as antigen-presenting cells (APCs) presenting myelin-derived peptides to T cells, leading to T cell activation and subsequent contribution to CNS inflammation (13). Another option considers that B cells produce proinflammatory cytokines, such as interleukin 6, which can then feed in the inflammatory process and contribute to disease (14, 15). Indeed, in the meninges of patients with secondary progressive MS, B cells have been shown to colocalize with T cells (16).

In PNAS, Sabatino et al. (3) identify an increased proportion of CD20+ T and B cells by anti-CD20 therapy in MS. Through presentation of CNS-derived antigens by APCs, naïve CD8+ T cells are primed in the lymph nodes. Along with plasma, CD4+ T, and CD20+ B cells, CD20+ effector memory CD8+ T cells transmigrate from the periphery through the inflammation-disturbed blood–brain barrier into the CNS. There they are reactivated by CNS APCs and clonally expand feeding inflammation. Anti-CD20 treatment by rituximab or ocrelizumab ablates both CD20+expressing CD8+ T and B cells but not Ig-producing plasma cells and CD20 T cells.

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*To whom correspondence may be addressed. Email: waisman@uni-mainz.de.
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perivascular space as well as in white matter lesions, noteworthy to a greater extent than CD4+ T cells (20). Additionally, they are present in cortical plaques of MS patients associated with disease progression, meningeal inflammation, and neurodegeneration (21).

Sabatino et al. (3) show that anti-CD20 treatment leads to the ablation of myelin oligodendrocyte glycoprotein-specific CD8+CD20+ T cells, demonstrating that this treatment in MS not only affects precursor and mature B cells but also CD8+ T cells. In conclusion, it is possible that the answer to why anti-CD20 is so effective as therapy for MS is simpler than previously thought, and its beneficial effects stem from elimination of pathogenic T cells and not B cells.

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