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Review

Memory B Cells are Major Targets for Effective Immunotherapy in Relapsing Multiple Sclerosis

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ABSTRACT

Although multiple sclerosis (MS) is considered to be a CD4, Th17-mediated autoimmune disease, supportive evidence is perhaps circumstantial, often based on animal studies, and is questioned by the perceived failure of CD4-depleting antibodies to control relapsing MS. Therefore, it was interestingly to find that current MS-treatments, believed to act via T cell inhibition, including: beta-interferons, glatiramer acetate, cytostatic agents, dimethyl fumarate, fingolimod, cladribine, daclizumab, rituximab/ocrelizumab physically, or functionally in the case of natalizumab, also depleted CD19+, CD27+ memory B cells. This depletion was substantial and long-term following CD52 and CD20-depletion, and both also induced long-term inhibition of MS with few treatment cycles, indicating induction-therapy activity. Importantly, memory B cells were augmented by B cell activating factor (atacicept) and tumor necrosis factor (infliximab) blockade that are known to worsen MS. This creates a unifying concept centered on memory B cells that is consistent with therapeutic, histopathological and etiological aspects of MS.

Contents

Abbreviations: AIDS, acquired immunodeficiency syndrome; APRIL, a proliferation-inducing ligand; BAFF, B cell activating factor; (BLyS), B lymphocyte stimulator; CNS, central nervous system; DMD, disease modifying drug; EAE, experimental autoimmune encephalomyelitis; EBV, Epstein Barr virus; Gd+, gadolinium-enhancing; HIV, human immunodeficiency virus; HSCT, hematopoietic stem cell therapy; IL, interleukin; mAb, monoclonal antibodies; MRI, magnetic resonance imaging; MS, multiple sclerosis; TNF, tumor necrosis factor.

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1. Introduction

Multiple sclerosis (MS) is the major inflammatory demyelinating disease of the grey and white matter of the central nervous system (CNS), leading to neurodegeneration and the accumulation of disability (Compston and Coles, 2002, 2008). It is clear that MS is a complex disease influenced by a large number of immune- associated genes, notably major histocompatibility complex class II alleles and sex chromosomes (Compston and Coles, 2008; Sawcer et al., 2014). However, the discordance between identical twins clearly indicates that any genetic susceptibility is heavily influenced by environmental influences (Compston and Coles, 2008). These include: a *geographical/latitude effect* relating to sunlight exposure; *lifestyle effects* including diet, education and smoking and an *infection effect*; virtually all people with MS have been infected with Epstein Barr Virus (EBV), which may be a key trigger in susceptibility to MS (Compston and Coles, 2002, 2008; Giovannoni and Ebers, 2007). Whilst pathology helps elucidate disease mechanisms (Compston and Coles, 2002, 2008) perhaps the most informative method is via the analysis of the response or lack of response to disease modifying drugs (DMD), with consideration to the trial design and implementation (Baker and Amor, 2014), and the adverse responses to DMD (Deiß et al., 2013; Marta and Giovannoni, 2012).

2. Inflammatory and Neurodegenerative Disease in MS

This approach to disease mechanisms often defines a two immune-compartmental model of MS (Fig. 1): (a) A peripheral compartment that drives relapsing disease and is associated with entry of mononuclear cells and plasma proteins into the CNS and (b) an intrathecal/CNS compartment that supports further white matter and grey matter demyelination and the loss of nerve circuitry that drives the neurodegeneration associated with progressive MS (showing deterioration without obvious relapses) (Lublin et al., 2014), and accumulating disability (Compston and Coles, 2002, 2008; Lublin et al., 2014). As such MS has been viewed as both an autoimmune and neurodegenerative disease requiring different treatments (Compston and Coles, 2002, 2008). However, these events are inter-related and occur concurrently from disease onset (Giovannoni et al., 2017) and it is clear that immunomodulation/suppression may be sufficient to control both relapsing and active progressive elements of MS (Steinman and Zamvil, 2016), which may slow deterioration to systems with sufficient neural reserve (Giovannoni et al., 2017; Steinman and Zamvil, 2016). However, pathology and responses to therapy indicate that targeting the peripheral component without change in the central compartment, is often insufficient to control more advanced worsening MS (Fig. 1) (Compston and Coles, 2002, 2008; Giovannoni et al., 2017). Thus, optimal disease control is likely to require neuroprotection and repair strategies in addition to immunomodulation to the limit the accumulation of disability (Compston and Coles, 2002, 2008; Giovannoni et al., 2017). Current DMD, largely target the peripheral immune component with the view of terminating focal inflammatory-relapse and/or magnetic resonance imaging (MRI) activity (Fig. 1) (Marta and Giovannoni, 2012). Although there is an increasing number of agents available to treat relapsing MS (Marta and Giovannoni, 2012; Martin et al., 2016), failure of trials by immunosuppressive agents was a common problem, until the methods to perform and monitor phase II (based on accumulation of gadolinium-enhancing (Gd +) T1 and new T2 lesions in MRI, respectively, and phase III trials (outcomes based on relapses) were improved and implemented (Compston and Coles, 2002, 2008; Marta and Giovannoni, 2012). For this reason many drugs failed, as they were tested in people with advanced progressive MS who respond poorly or too slowly to immunosuppressive agents that control inflammatory relapsing MS (Coles et al., 1999; Compston and Coles, 2002; Giovannoni et al., 2017). This is best seen with hematopoietic stem cell therapy (HSCT) where treatment is most effective in people with active inflammatory disease with Gd + lesions and clinical relapses (Atkins et al., 2016; Burt et al., 2015). This suggests that once neurodegeneration is triggered within a neural circuit, probably through innate immune activation, it may no longer respond to the therapies that halt the relapses that trigger the damage (Compston and Coles, 2002; Giovannoni et al., 2017; Hampton et al., 2013). This neurodegenerative process is detectable from the initial attacks (De Stefano et al., 2010; Giovannoni et al., 2017), but clinical progressive deterioration may only become noticed once the compensating neural reserve within affected pathways become exhausted (Giovannoni et al., 2016a, 2017). This can occur early as in primary progressive MS or following a number of attacks in secondary progressive MS (progressive worsening following a period of relapsing attacks) (Compston and Coles, 2002; Giovannoni et al., 2016a; Lublin et al., 2014). Importantly, this argues for early and effectively treatment to maintain brain health (Giovannoni et al., 2016a).

3. T Cell-specific Immunotherapies Have Proved Ineffective at Blocking Relapsing MS

The question remains about the nature of the peripheral target for immunotherapy. There is abundant evidence to suggest that MS is a mainly CD4 Th1/Th17 T-cell mediated disease (Martin et al., 2016). This concept is largely based on autoimmune experimental encephalomyelitis (EAE) studies in animals (Martin et al., 2016; Rostami and Ciric, 2013; Volpe et al., 2015). Surprisingly whilst all treatments that affect MS can influence T cell function and T cell subset distribution (Martin et al., 2016), clinical trial data with specific CD4, Th1/Th17 immunotherapies have all largely failed to exhibit more than marginal impact on relapsing MS (Deiß et al., 2013; Segal et al., 2008; van Oosten et al., 1997). This may argue against a significant role for CD4 T cells in the control of MS. However, CD4-depletion studies were undertaken when HIV/AIDS mechanisms uncovered the risks of CD4 lymphopenia, therefore deletion was targeted to maintain CD4 T cell numbers above 250 cells/μL. Although there was some effect on relapse rate, the trials failed to show an effect in reducing new MRI lesion formation, with about a 60–70% CD4 T cell depletion (van Oosten et al., 1997). In the animal model, >85% CD4 T cell depletion inhibits EAE and depletion of 30% exhibits essentially no effect, whereas about a 60% depletion exhibits a marginal effect in an optimized system (von Kutzleben et al., 2016). This therefore creates a concern that the human studies failed to deplete sufficiently to control disease.

Likewise, blockade of interleukin (IL)-12 and IL-23 with ustekinumab to inhibit Th1 and Th17 did not significantly affect the MRI lesion load in MS (Segal et al., 2008). Again, whilst blockade of IL-

Fig. 1. Two immune-compartment model of multiple sclerosis. The initial trigger of the lesions is due to: (a) peripheral sensitization due to molecular mimicry or another event in the lymph node (outside-in) or (b) oligodendrocyte damage leading to liberation of antigen proteins or peptides that exit via the glymphatics to draining lymph nodes (inside-out) where autoreactive lymphocytes are sensitized. A. 1. Primed T and B cells are generated and travel round the body. 2. Immune cells enter into the CNS. 3. Following recognition of a target presented by a perivascular microglial (Mi) cell there is local activation of the infiltrating lymphocytes. 4. Cytokine release occurs to activate the blood brain barrier to express adhesion molecules. 5. A second wave of influx of T cells, B cells and monocytes enters the CNS. 6. These cause damage to the oligodendrocyte (O) via release of antibodies, and soluble products and possibly by direct killing by cytotoxic T cells (Tc). 7. Demyelinated nerves (N) have an elevated energy requirement to maintain neurotransmission. These are vulnerable to excitotoxic and other damage elements such as by activated microglial cells, and B cell products. 8. Microglial and B cells are sequestered into CNS compartment. B. Current DMD prevent entry of the peripheral adaptive immune cells into the CNS. This will block relapsing disease allowing natural repair mechanisms to act and induce a long-term status of no evidence of disease activity. C. These events produce an innate inflammatory environment formed from glial cells and adaptive immune niches, such as B cell infiltrates are created within the CNS. These may not responsive to peripheral immune control and may allow neurodegeneration and accumulation of disability to continue in the absence of active lesion formation.