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Is there a place for 'immuno' in the immunotherapy of multiple sclerosis?

"...even with all the apparent initial success of immunomodulatory treatments, the contribution of neural and glial degenerative processes to the pathogenesis of progressive multiple sclerosis needs to be carefully considered and studied..."

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Multiple sclerosis (MS) is an often devastating disease of the CNS that affects approximately one out of every 1000 people in the USA and an estimated 3 million subjects worldwide, with a predominance of female patients [1–3]. During the first few years following clinical onset, the majority of patients suffer from the relapsing–remitting form of MS, which is characterized by attacks of neurological dysfunction followed by recovery periods of various lengths. After 10 years, approximately half of the relapsing–remitting patients have entered the secondary-progressive form of MS, whereby the disease continues to get worse without intermittent recovery. Currently, there is no cure for MS and available treatments improve acute disease but have demonstrated little effect on preventing progression to disability. Progress in development of therapies is expected to be made from a good understanding of the mechanistic concepts underlying the pathogenesis of the disease. Along these lines, it is unknown what causes MS, but it is widely believed that, for unknown reasons, the immune system launches an erroneous attack on the CNS, which in turn leads to demyelination and axonal degeneration [2–4]. This view is supported by the salient histopathological features of MS that encompass varying degrees of inflammation with perivascular, intraparenchymal and meningeal cellular infiltrates consisting of $CD4^+$ and $CD8^+$ T cells, macrophages, B cells and plasma cells, as well as demyelination, gliosis and axonal loss [5–7]. Further evidence comes from the genetic association of MS with immune response genes, the strongest and longest known being for the human HLA-DR2 haplotype [8–9] and, as more recently revealed, for the IL-7 receptor α-chain [10]. MS can be mimicked in animal models by injection of CNS antigens termed experimental autoimmune encephalomyelitis (EAE), and some T-cell receptor (TCR) transgenic mouse models develop spontaneous autoimmune disease [11].

However, there are dissenting views on the role of the immune system in the pathogenesis of MS, with some emphasizing the hypothesis of a primary neurodegenerative component [12]. Arguments that have been raised are that CNS pathology in MS is not always associated with inflammation, that it is often difficult to detect T-cell responses to neuroantigens in MS patients (which are also found in healthy control subjects), and that the genetic associations with immune function genes is relatively weak. Furthermore, EAE may not be a perfect model of MS, but rather a model for acute CNS inflammation [13].

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Amidst these controversial views, data from the laboratory of life, in other words, several clinical trials in MS patients, may have provided the most ardent support for the contribution of the immune system to promoting pathology in MS. First, Bielekova and colleagues at the US NIH and Kappos and colleagues used altered peptide ligands of the human myelin basic protein peptide 83–99 (MBP83–99) to attempt to silence the pathogenic T-cell response [14,15]. While, unfortunately, both clinical trials failed, the NIH study found that the treatment enhanced the severity of clinical disease, which was paralleled by enhanced neuroantigen-specific T-cell responses, thus strongly implicating neuroantigen-reactive T cells in MS. Further compelling support for immune system involvement comes from Phase I or II clinical trials of

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immune suppression and autologous bone marrow transplantation that demonstrated in the majority of patients with severe-relapsing MS, a complete suppression of exacerbations and development of new lesions detected by MRI [16]. Last but not least, the evidence summarized by Croxford and Yamamura in this issue of *Immunotherapy* clearly shows that targeting one or more critical components of the adaptive and/or innate immune system in patients with MS can result in substantial amelioration of the clinical course [17].

The list of widely available immunomodulatory treatments includes IFN-β preparations, glatiramer acetate and natalizumab. IFN-β may act via antiviral effects, by interfering with immune cell trafficking and deactivating them in the CNS, and copaxone may anergize pathogenic $CD4^+$ T cells on the one hand and induce regulatory $CD8^+$ T cells on the other hand [18]. Natalizumab, which targets VLA-4, an adhesion molecule necessary for migration of immune cells into the CNS, is currently the most rapidly and potently acting immune-modifying treatment and is generally well tolerated. Additions expanding the list of approved immunotherapies are expected in the next few years. Alemtuzumab (formerly known as Campath-1H) is very effective at suppressing inflammation, and its administration in early MS can promote recovery of neurological symptoms. Rituximab, which depletes B cells, is somewhat enigmatic because it also shows almost immediate efficacy, which argues against a role for antibodies in MS and towards a significant effect of antigen presentation by B cells.

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As a common theme, all these drugs either target migration of immune cells into the CNS, or downregulate the function of pathogenic cells, possibly by depleting them, by decreasing cytokine production or antigen presentation. If one were to venture a guess, keeping immune cells out of the brain or keeping them silent in MS appears to be clearly beneficial for acute episodes of the disease. However, there is also a darker side to this generalist approach: adaptive and innate immune cells are indispensible in keeping unwanted guests out of the brain, such as infectious microorganisms, and preventing stealthy residents from taking over such as CNS latent viruses. Fatal progressive multifocal leukoencephalopathy induced by the John Cunningham (JC) virus infection in natalizumab-treated patients is one such example of the risks associated with a strict no-access to the CNS policy enforced by some immunomodulatory treatments. Further concern arises from the observation that natalizumab continues affecting immune cells for months after termination of treatment. Of course, a way of turning off undesired immune responses at will and turning on protective immunity may resolve these concerns. Thus, there is certainly some room for improvement, both in our theoretical underpinning of the underlying mechanisms of MS and in the currently available treatment modalities.

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A critical issue is the failure of current treatments to prevent long-term progression to disability. Here, therapy already fails at the conceptual stage, since we do not know what the underlying mechanisms are. Is there continuous involvement of the immune system that drives disability? Is the initial noxious 'hit' sufficient to drive the myelinating cells or their precursors and neurons into persistent self-destructing madness, or is it microglia that cannot return to a restful homeostatic balance? Are adaptive or innate immune cells even useful to the repair of the CNS after an attack of MS? The latter is suggested by the dual role of cytokines such as TNF-α that initially promote CNS damage via TNFR1, but subsequently are indispensible for repair via TNFR2 [19]. In other words, keeping inflammatory cells out of the CNS initially may come at a cost later on. As disease detectives, should we consider that the failure of immunomodulatory treatments at preventing long-term disability may even suggest we are on the wrong track after all and that the immune system is an innocent bystander? At least, we should acknowledge that we cannot draw final conclusions on the role of the immune system on the development of neurodegeneration before having tested truly effective immunotherapies, that are started early enough in the disease course, and having followed patients long enough with appropriate outcome measures. Until then, even with all the apparent initial success of immunomodulatory treatments, the contribution of neural and glial degenerative

processes to the pathogenesis of progressive MS needs to be carefully considered and studied in the laboratory and in clinical trials.

The readers will find twofold value in the review article by Croxford and Yamamura published in this issue of *Immunotherapy* [17]. Immunologically minded folks will find food for thought to reflect on how immune manipulation can modify the course of MS inflammation. The more clinically minded reader will find a timely and practical summary of the state of the art on disease-modifying therapeutics that are approved or being developed for MS. In either case, it is a paper well worth reading.

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