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Commentary

The complex etiology of multiple sclerosis

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ABSTRACT

Multiple sclerosis is a demyelinating disease which is presumed to be a consequence of infiltrating lymphocytes autoreactive to myelin proteins. This is substantiated by several lines of clinical evidence and supported by correlative studies in preclinical models. The development of new therapeutics for MS has been guided by this perspective; however, the pathogenesis of MS has proven to be quite complex as observations exist which question the role of autoreactive lymphocytes in the etiology of MS. In addition the current immunomodulatory therapeutics do not prevent most patients from progressing into more serious forms of the disease. The development of truly transformational therapeutics for MS will likely require a broad assault that expands beyond the concept of MS being an autoimmune disease.

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1. Introduction

It is often tacitly assumed that multiple sclerosis (MS) is an autoimmune disease involving multifocal areas of brain lesions which contain axons demyelinated due to the initiation of an inflammatory response associated with the recruitment of lymphocytes autoreactive to myelin proteins [1]. The immunological data underlying this position include the isolation of myelin protein-reactive T cell clones from MS patients [1,2], the cytokine profile of these T cell clones which is consistent with a delayed type hypersensitivity (DTH) reaction believed to be a hallmark of autoimmune diseases [3], the demonstration of tissue destruction and axonal demyelination in rodents by myelin-reactive T cells from transgenic mice harboring the T cell receptor for an immunodominant epitope from myelin basic protein (MBP) deduced

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Abbreviations: MS, multiple sclerosis; DTH, delayed type hypersensitivity; RRMS, relapsing, remitting multiple sclerosis; EAE, experimental autoimmune encephalomyelitis; MRI, magnetic resonance imaging; EDSS, expanded disability status scale; MBP, myelin basic protein; PLP, proteolipid protein; MOG, myelin oligodendrocyte glycoprotein; Th-1, T helper cell type-1; OCBs, oligoclonal bands; CSF, cerebrospinal fluid; IFN-β, beta-interferon; IFN-γ, gamma-interferon; Th-2, T helper cell type-2; VLA, very late antigen; MHC, major histocompatibility complex; HLA, histocompatibility leukocyte antigen; Th-17, T cells producing IL-17; PBMCs, peripheral blood mononuclear cells; qRT-PCR, quantitative real time-polymerase chain reaction; MSRV/HERV-W, MS-associated retrovirus/human endogenous retrovirus W; HHV-6, human herpesvirus-6; EBV, Epstein–Barr virus; SIP-1, sphingosine-1-phosphate; CB_1, cannabinoid receptor type 1; CB_2, cannabinoid receptor type 2; ROCK, rho-associated kinase; Kv, voltage gated potassium channel; T_{em}, memory effector T cells; HSCT, hematopoietic (bone or bone-marrow derived) stem cell transplantation; hESCs, human embryonic stem cells

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from T cell clones isolated from MS patients [4], the recapitulation of disease symptoms in laboratory animals following adoptive transfer of MBP-reactive lymph node cells [5], and the immunomodulatory effects of approved therapeutics showing clinical benefit in MS patients [3]. This autoimmune phenotype is felt to be reflective of most MS patients, classified as having relapsing/remitting disease (RRMS), and may even set the stage for the more rapidly progressive forms of MS (e.g., primary progressive, secondary progressive), where neurological deficit continues largely independent of any signs of the inflammatory based lesions [6].

This autoimmune profile and the associated biochemical pharmacology have been important drivers in drug discovery programs directed towards developing more effective therapies for MS. Included in these drug discovery approaches is the evaluation of prospective drugs in the primary animal model for MS, experimental autoimmune encephalomyelitis (EAE), which is constructed either by immunization with myelin antigens or via adoptive transfer of myelin protein-reactive T cells [1,3–7]. Importantly, currently marketed therapies for MS show efficacy in these EAE models [7]. Since the model is an important part of the decision tree in MS drug discovery programs, it is not surprising that most, if not all, current clinical trials for MS are with compounds targeting the purported altered immune/inflammatory response [8].

However, scrutiny of the clinical progress of treated patients shows disappointing results for the current therapies with regards to halting disease progression [6,9]. Moreover, observations from several groups have led to the appreciation that MS has a very complex etiology (e.g., [10]) which has lead to a questioning of the tacit assumption that MS is indeed an autoimmune disease [6,11]. Questioning the autoimmune etiology of MS is not new [12] and has led some to postulate that MS may be a heterogeneous syndrome with at least the more progressive forms of the disease harboring a different, non-autoimmune etiology [13]. This commentary critiques the data which support and are at odds with the autoimmune etiology of MS and, in so doing, questions the logic of 'staying the course' in the pursuit of new and effective drugs for all forms of MS. More effective therapeutic regimens for MS patients will require creative approaches to limit fulminating inflammatory responses and also quell the neurodegenerative processes operant even in the early forms of the disease.

2. MS as an autoimmune disease

There are several lines of evidence to support the long-held belief that MS is indeed a disease with an autoimmune etiology.

2.1. *Pathophysiology: an altered immune response*

Numerous clinical observations support the position that MS is an autoimmune-driven disease. A key pathological finding in MS patient brains is the presence of diffuse, inflammatory plaques, primarily in the white matter and also now appreciated to extend into the gray matter [3,6,10]. The plaque contains an inflammatory cellular infiltrate, dominated by T cells and macrophages, and can contain areas of axonal demyelination, gliosis and loss of both axons and oligodendrocytes.

Acute lesions are likely the pathophysiological correlate of the clinical relapse in RRMS [14] although magnetic resonance imaging (MRI) techniques have demonstrated the appearance of far more lesions than suggested by monitoring clinical observations. This may reflect symptomatically silent areas of the brain which harbor some of these lesions, compensatory neuronal circuitry and/or insufficient demyelination to effect any clinical syndrome [6,14]. Thus, MRI offers a valuable mechanism for ostensibly assessing progression of disease which may not necessarily be correlated with clinical scores such as the expanded disability status scale (EDSS). Lesioned areas do have the capacity for remyelination which may not only counter inflammatory-initiated demyelination but also underlie remission following a relapse. However, over time, possibly years, this capacity wanes with resulting progression of the disease characterized with a more serious neurological deficit associated with neuronal dysfunction and axonal degeneration [3,6,14].

Several groups have demonstrated a robust lymphocytic activation response to myelin associated proteins (e.g., MBP [2], proteolipid protein (PLP) [2,15], myelin oligodendrocyte glycoprotein (MOG) [2,16] and myelin-sequestered alpha B crystallin [17]) in cellular preparations isolated from blood and brain tissue from MS patients, lending credence to the presence of an altered autoimmune response. When isolated, the myelin protein-reactive T cell clones typically elaborate a T helper cell type-1 (Th-1) cytokine profile upon activation with the myelin protein antigens, an anticipated response should autoreactive T cells be involved in the pathophysiology [1,14]. Activated CD4+ T cells, isolated from MS patients, release more of the proinflammatory cytokine IL-17 compared to cells isolated from healthy donors [18], and transcripts of IL-17 were found to be elevated in brain lesions from MS patients compared to controls [19]. CNS lesions associated with an inflammatory infiltrate, and axonal demyelination, occur following the adoptive transfer of myelin protein-reactive T cells in EAE (e.g., [5]). Moreover, administration of an inadvertent encephalitogenic peptide of MBP to MS patients led to an exacerbation of disease [20].

An important diagnostic criterion for MS is the sign of increased intrathecal synthesis of immunoglobulins as detected by oligoclonal bands (OCBs) in samples of cerebrospinal fluid (CSF) [21]. The presence of these bands suggests an increased B cell response to brain resident antigen(s) [3,6]. The absence of these OCBs upon diagnosis has been reported to be associated with a less severe disease progression [21].

2.2. *Immunomodulators effective as therapeutics*

Although the exact mechanisms of action for the immunomodulatory drugs marketed for MS remain controversial, several (e.g., beta-interferon, glatiramir acetate and natalizumab) have been shown to be effective in limiting relapses as well as the development of new inflammatory lesions [1,3,14]. The logic for the use of beta-interferon (IFN-β; Avonex®, Rebif® or Betaseron®) in MS was, in part, spawned by findings that administration of gamma-interferon (IFN-γ) to patients

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