Multiple Sclerosis – is the Autoimmune Reaction all Smoke and Mirrors?

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Abstract

The most widely accepted hypothesis of MS pathogenesis is the autoimmune hypothesis. Recently, an alternative theory based on neuropathology of acute MS lesions has been proposed that may argue against the autoimmune hypothesis. It suggests that the initial pathology is oligodendrocyte apoptosis, while the subsequent inflammation that is "autoimmune-like" may in fact be a secondary phenomenon. This new evidence of a potential pathogenesis may have major implications in terms of treatment options. Instead of using Disease Modifying Treatments (DMTs) we can focus on targeting the initial oligodendrogliopathy and therefore halt the progression of disease before it starts.

Introduction

When asked what causes Multiple Sclerosis (MS) by our patients, almost by reflex, medical students and doctors alike answer that it's an autoimmune disease that leads to the loss of neural functions[1,2]. The idea of molecular mimicry, a phenomenon of self-directed immunity by microbial epitopes[3], has been implicated as the initiating trigger that results in an autoimmune reaction. The autoimmune hypothesis has dominated MS research since the late 1950s[4], so much so that biotechnology companies have solely focused drug treatment options on autoimmunity and inflammatory targets[3]. Although this theory has been accepted for over 50 years it has never been proven, nor the initiating events elucidated[2]. Novel studies using neuropathology have implicated a potentially new pathogenesis and hypothesise that MS is an oligodendrogliopathy disease[4] in which the inflammatory response may in fact be secondary to the apoptosis of oligodendrocytes (OLs). OLs are the myelinating cells of the central nervous system[5], and play a critical role in brain development and neuron function[6].

It has been suggested that MS may even be a heterogeneous disease that encompasses both pathologies of autoimmunity and oligodendrogliopathy[7]. The idea that there is a variation in the pathology could not only shift diagnostic approaches for MS, but also shift treatment focus towards novel therapeutic strategies that protect oligodendrocyte progenitor cells (OPCs) and rescue mature myelinating OLs from apoptotic triggers[1]. The implications of this could be life-changing for the 2.5 million individuals[8] that are currently afflicted with this debilitating disease.

The Autoimmune Hypothesis

The most popular theory linking autoimmunity to MS is that there is a triggering infection caused by a microbe that induces molecular mimicry[9]. The theory is that naïve myelin antigen-specific CD4-positive T-cells are primed in the peripheral lymph nodes by dendritic cells, or antigen presenting cells, which present myelin or myelin cross reactive epitopes. Once these primed T-cells (now Th17 cells) penetrate the CNS parenchyma and are reactivated by macrophages that express myelin epitopes, they secrete cytokines that are toxic to the myelin and induce demyelination[10]. Essentially, it is thought that the mechanism responsible for myelin destruction involves CD4 T-cell-dependent macrophage activation directed against a myelin or OL antigen[11-14]. Therefore, the autoimmune theory proposes that our immune system is problematic, with an influx of immune and inflammatory cells that ultimately causes demyelination and neuronal death. Although one may wonder if our highly intricate immune system can be so easily duped into destroying our own neural network, there is precedence for such a scenario. *Campylobacter jejuni*, for example, is the causative agent in inducing molecular mimicry in acute motor axonal neuropathy, a subtype of Guillain-Barré syndrome[15,16].

In terms of MS, a prevalent hypothesis is that a virus causes this "hit-and-run" molecular mimicry[3]. It has been

Clinical Points

- Multiple Sclerosis (MS) is an immune-mediated demyelinating disease of the human central nervous system (CNS).
- The autoimmune hypothesis of aetiology of MS has yet to be proven and it still remains to be determined if inflammation is a primary or secondary event in the degenerative process.
- A novel oligodendrogliopathy hypothesis demonstrates that apoptotic cell death of oligodendrocytes (OLs) may be the initial event in new MS lesion formation as well as the initiator of inflammation in acute MS.
- Failure of remyelination after an acute attack may occur due to OL and oligodendrocyte precursor cell (OPC) death, and the inability of OPCs to differentiate into myelinating OLs.
- The focus of treatment may be shifted to an approach that targets this initial olidodendrogliopathy rather than disease modifying treatments (DMTs) that focus on inflammatory molecules, which may in fact be a consequence rather than a trigger of MS.

noted that the protein sequence on some viral proteins present a homology with an autoantigen sequence in the CNS, such as the Hepatitis B virus (HBV). The viral protein in HBV is homologous with a segment of myelin basic protein[17], a protein believed to be important in the process of myelination[18], but to date, no virus has been unequivocally implicated. However, even with a hypothesis that a virus can be implicated in MS, one must keep in mind that both viral infections and autoimmunity can induce T-helper cell type 1 inflammation and consequently similar signalling pathways. Therefore, could our focus on autoimmune theories of MS be clouding the possibility that the viral infection itself could instead be inducing OL apoptosis and oligodendrogliopathy[3]?

The Oligodendrogliopathy Hypothesis

The hypothesis of oligodendrogliopathy suggests that primary OL death causes the demyelination. The subsequent inflammatory response that appears to be "autoimmune-like," may in fact be a mere epiphenomenon that acts to clear away the myelin debris that is present from the demyelination[4]. The oligodendrogliopathy hypothesis arose from neuropathological studies of MS lesions, but due to the rare occurrence of rapidly disabling and consequently fatal MS lesions[3] there is difficulty in obtaining appropriate MS specimens. As a result, studies that utilise human tissue affected with MS are far less reported than those that use experimental autoimmune encephalomyelitis (EAE). EAE is the animal autoimmune model for MS[4] and the experimental foundation upon which the autoimmune theory is based.

One such study that provided pathological examples was conducted by Lucchinetti *et al* in 2000. It suggested that MS may have heterogeneous pathological mechanisms, and it was noted that there were two patterns with the characteristic autoimmune pathology as well as two patterns with an oligodendrogliopathy pathology[7]. These four patterns of demyelination that were found were heterogeneous between patients, but homogenous within each individual patient, indicating that disease pathogenesis does not change within a single patient[7]. Although this study may demonstrate heterogeneity of MS, in both its causation and course, it is also possible that the four different pathological pictures may only reflect differences in the timing of the biopsy or autopsy[4]. It would be interesting to see if these lesional patterns remain constant throughout the duration of the disease course, or if they change as time progresses and the disease changes from acute to chronic phases.

In 2004, Barnett and Prineas analysed several MS lesions, with the earliest autopsy case being only 17 hours after the onset of symptoms[19]. These cases were exceptionally acute cases and provided a unique insight on the pathology of relatively newly diagnosed lesions. In all 10 lesions, the earliest structural change that was shared was extensive OL apoptosis and early microglial activation, but few or no infiltrating lymphocytes or myelin phagocytes were present[19]. This study implies that the initial event in MS lesions is apoptosis of OLs, as opposed to an autoimmune insult.

In a separate study done by Henderson *et al* in 2009, twenty-six active lesions from 11 patients with early MS were serially sectioned and immunostained. In the sections stained, parenchymal T- and B-cells were mostly absent in areas of *initial* OL loss, as well as in areas of degenerate and dead myelin infiltrated by myelin phagocytes. However, areas of *complete* demyelination, which were packed with lipid macrophages and in some lesions regenerating OLs, revealed large numbers of T- and B-cells and IgG-positive plasma cells. These results demonstrate that the prominent feature in rapidly expanding MS lesions is the early loss of OLs, while macrophage activity is simply a scavenging response to the dead and degenerate myelin. The T- and B- cells seem to appear later in response to recently demyelinated tissue[11]. Perhaps these immune responses are not toxic but permissive for oligodendroglial regeneration and remyelination[4]. This suggestion supports the evidence found in experimentally demyelinated animals which demonstrated that when there is remaining myelin debris, remyelination is impaired[20]. This is yet another implication that lesion formation in MS may have some other basis other than destructive cell-mediated immunity directed against a myelin or OL antigen[11].

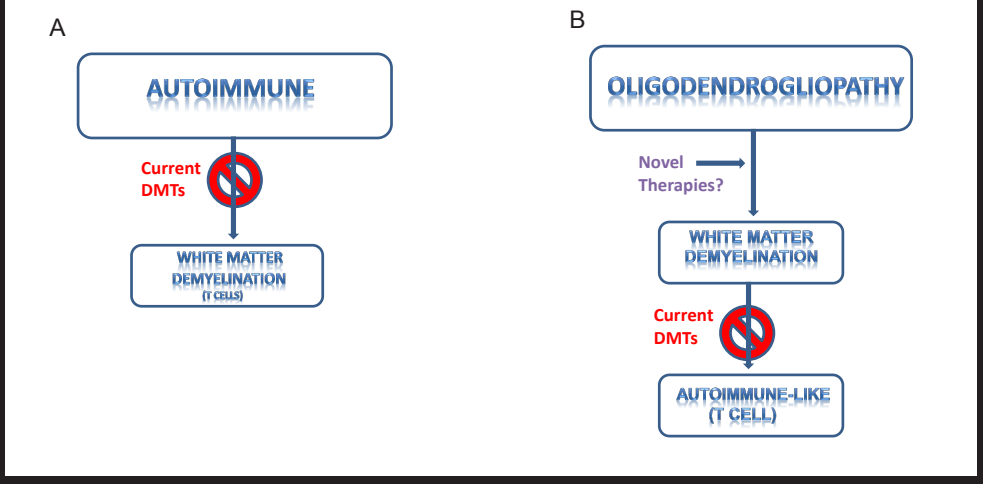

Fig 1: The two hypotheses and their relation to DMTs. (A) the autoimmune hypothesis and (B) the oligodendrogliopathy hypothesis. Current DMTs are designed to primarily target T-cells. Therefore, the development of new treatments that inhibit oligodendrogliopathy may result in a better clinical outcome if the latter hypothesis holds true[4].

What causes the Oligodendrogliopathy?

Possibilities for the aetiology of demyelination include a viral infection of the OLs[3, 7, 21], hypoxia stress secondary to ischemia, an immune-mediated vascultis[22,23], or lastly, secretion by activated microglia of cytokines that have shown to selectively damage OLs[24].

Nakahara *et al* reveals some insight regarding remyelination. In previous studies, it has been shown that there is a differentiation block in the OPCs which is a major determinant of remyelination failure in MS[25]. Nakahara *et al* demonstrated that the TIP30 protein, a proapoptotic protein, is abnormally over expressed in OPCs in chronic MS lesions. This overexpression arrests differentiation into mature OLs, thereby causing the pathogenesis of remyelination failure[26]. Unfortunately, this study does not address the initial causation of demyelination, which still remains to be shown.

MicroRNAs-a novel treatment for a novel hypothesis?

Alternate mechanisms are important when considering treatments, as theoretically MS patients with oligodendrogliopathy type lesions may not fully respond to current disease modifying therapies (DMTs)[4]. One current example, Alemtuzumab, uses a humanized monoclonal antibody that targets an antibody on all mature lymphocytes and consequently depletes all T- and B-cells, including auto-reactive lymphocytes[27]. Therefore a therapy that may be useful for patients with one form of the disease may in fact be suboptimal in another[7].

Alternatively, it may be useful to focus on new approaches of treatment that target the preservation of OLs as well as induce their remyelination. Recently it has been shown that MicroRNAs (miRNAs) may be novel regulators of OL differentiation and myelin maintenance. They do this by inhibiting negative genes that maintain the undifferentiated state of OPCs, thereby increasing the number of OPCs and subsequently OLs, resulting in remyelination[6].

Conclusion

The biggest challenge for both researchers and patients is to understand the cause of MS. Even though both of these hypotheses provide much insight, they are still largely unproven. Are these two theories describing completely different pathologies of the disease? Can they be unified into one theory to explain the entire disease course? Is it possible that MS is not an autoimmune disease caused by an environmental factor, but instead what appears to be the autoimmune response could just be a secondary phenomenon? Perhaps it is time to think outside the box with an investigative frame of mind rather than support a long-standing hypothesis of autoimmunity that has been so difficult to prove.

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