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Editor

Advances in Multiple Sclerosis and Experimental Demyelinating Diseases

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Cover Illustration: Remyelination-promoting antibodies that bind to oligodenrocytes, from left to right: mouse model, rat model, human

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Preface

There is a need for a paradigm shift in our thinking about the pathogenesis of multiple sclerosis (MS). From the days of Charcot in the 1800s, MS has been pathologically characterized primarily by demyelination; that is, the loss of myelin with the relative preservation of axons. Early manuscripts emphasized the inflammatory component, but in many cases, this was not thought to play a major role in the pathogenesis.

At the present time, the prevailing concept in MS is that the inflammatory response is critically involved in the destruction of the myelin sheath. This is derived from relatively weak data in humans but primarily based on an experimental model of MS known as experimental autoimmune encephalomyelitis (EAE), in which animals are immunized with myelin antigens. These animals usually develop a monophasic disease characterized primarily by inflammation and the relative absence of demyelination. More recently, this experimental model has demonstrated clear evidence of demyelination. This has mostly occurred as a result of the adoptive transfer of antibody directed against one of the myelin-specific proteins, myelin oligodendrocyte glycoprotein (MOG).

However, after more than 100 years of investigation into this disease, there still is no diagnostic clinical test dealing with the immunology of MS to support the autoimmune hypothesis. This is in contrast to a disease related to MS, neuromyelitis optica, in which patients develop an antibody directed against aquaporin 4 (see the chapter by B.G. Weinshenker and D.M. Wingerchuk). In this situation, there is evidence that autoimmunity plays a major role. This is not surprising in that neuromyelitis optica, for a very a long time, has been associated with other autoimmune disorders. Specifically, patients with neuromyelitis optica frequently develop antibodies against native DNA, antinuclear antibodies, and antibodies to other autoantigens. Unfortunately, similar assays done in MS have failed to reveal a specific antibody associated with the disease. Even the most recent attempts to associate antibodies to myelin basic proteins or MOG to disease progression have not been replicated by a number of investigators. MS is not associated with other autoimmune diseases. At this point in time, there is insufficient evidence to consider MS an autoimmune disease.

If the disease is not autoimmune in nature, then what is the basis of its pathogenesis? In an effort to begin to understand this, it is important to go back to the roots of neuropathology. The neuropathology of this disease has been revisited (see

the chapter by C.F. Lucchinetti). It is clear that there are different subtypes of MS; at least four have been identified. Two of these are diseases in which myelin appears to be the primary target; in the other two subtypes, the disease appears to be directed against the cells that make the myelin sheaths, the oligodendrocytes. Even in those subtypes in which myelin sheaths are the primary target of injury, there is still loss of 30% of oligodendrocytes, which suggests that early oligodendrocyte injury may be common to all forms of MS. If early oligodendrocyte injury is a prerequisite to MS, then what is the basis of this injury? A number of possible scenarios come to mind in view of the experimental models. Clearly, viruses are high on the list because a number of viruses have been shown to induce demyelination in animals as well as in humans (see the chapters by A.J. Bieber and by A.E. Warrington and M. Rodriguez). In particular, infection with viruses of many different families results in well-demarcated areas of demyelination in association with variable axonal loss. In addition, toxins such as cuprizone or Lysolecithin (see the chapter by W.F. Blakemore and R.J.M. Franklin) also appear to cause dysfunction of oligodendrocytes and induce very focal areas of demyelination. Finally, demyelination may result from a genetic defect that affects oligodendrocyte function. In most of these known genetic disorders, the disease manifests before myelin completely forms, and therefore, these diseases are called dysmyelinating in nature. However, in adrenoleukodystrophy, the myelin begins to degenerate after it has been completely formed. This known genetic disorder of lysosomes clearly shows evidence of inflammation as well as areas of demarcated demyelination. Therefore, it is possible that a genetic abnormality is the initial driving event in the oligodendrocytes that predisposes to long-term demyelination.

Clearly, we may not be able to identify the very early event that initiates MS, since it may occur decades before clinical presentation. However, by understanding the effector molecules initiating the demyelination process, we may be able to intervene in the disease therapeutically. What has become clear in the last few years is that one of the most important effector cells in the MS lesion is the $CD8^+$ T cell. In contrast to previous thought, which has focused primarily on the role of $CD4^+$ T cells in EAE, $CD8^+$ T cells are usually cytotoxic in nature. While some have been shown to perform a regulatory function in the immune system, many of these cells are cytotoxic in nature and recognize class I MHC antigens on the surface of cells. It was once thought that class I MHC antigens were not expressed in the central nervous system (CNS); however, recent evidence suggests that class I antigens are expressed in many of the cell types including oligodendrocytes, astrocytes, microglia, axons, and neurons. In experimental models of demyelination, class I antigens are expressed very early after the induction of virus infection. It is well known that viruses can cause the elevation of class I MHC in the CNS. It is likely that the mediators of the generation of class I MHC in the CNS are the interferons. If $CD8^+$ T cells play a major role in the disease process, then what do they recognize? It is clear that $CD8^+$ T cells recognize peptides that have been processed within the cell by macrophages or microglia. These are usually eight to ten amino acids in length. They can encompass parts of the host cell as well as exogenous factors such as

viruses. It is possible that many antigens are presented in the context of class I MHC in the MS lesion to be recognized by $CD8^+$ T cells. It is interesting to note that experiments in the models of MS induced by viruses indicate a clear immunodominance of peptides recognized by $CD8^+$ T cells. In some experimental models, up to 60% or 70% of the $CD8^+$ T cells are directed against one specific immunodominant peptide. This provides a very interesting target for preventing the demyelinating process by immunotherapy. Unfortunately, it is difficult to isolate $CD8^+$ T cells from MS brain or CSF and even more difficult to culture these cells to a significant number to allow for identification of the peptides recognized by these cells.

The other aspect of immune response critical to demyelination is immunoglobulin. Immunoglobulins are the hallmark of the clinical assays used to diagnose MS. MS patients are known to have oligoclonal IgG and IgM bands in the CSF. These oligoclonal bands are directed against a relatively small number of antigens. Efforts have been made to identify the antigens recognized by these antibodies. In experimental models and viral diseases of humans demonstrating oligoclonal bands, the oligoclonal bands are directed against the infectious agent. It is possible that the same process may be occurring in the MS plaque. Therefore, continuing efforts to identify the antibodies' target are extremely important. The other possibility is that these antibodies are part of a natural immune response important in the reparative process in MS (see the chapter by A.E. Warrington and M. Rodriguez). If this is the case, then these antibodies are reparative in nature and may be part of the natural immune response that promotes remyelinating activity.

What has also become apparent is that remyelination is a common event in the MS plaques. Efforts to enhance remyelination in MS have not yet been attempted clinically. Some investigators believe that the progenitor cells within the MS plaque are depleted; therefore, it would be necessary to transplant either stem cells or purified populations of oligodendrocytes into the MS plaques for remyelination to take place (see the chapter by W.F. Blakemore). Other investigators believe that the progenitor cells are present in MS plaque; therefore, approaches to trigger remyelination by these cells are potential mechanisms of treatment (see the chapter by A.E. Warrington and M. Rodriguez). Most recently, studies have recognized natural autoantibodies directed against oligodendrocytes, and these demonstrate remarkable remyelination when used as treatment in experimental models of demyelination. These natural autoantibodies have been cloned and sequenced and appear to have genetic sequences very close to the host germline sequences. These antibodies, therefore, are called natural autoantibodies, since they are directed against host-cell proteins and are present as part of the normal repertoire. Work with a human recombinant IgM antibody, isolated from a human designated 22, is nearing the late phase of completion of animal experiments and may soon be ready for application in human trials. This would be the first attempt to enhance remyelination in the MS lesion and a completely different approach to the present MS treatments. In this case, the therapies would target the cells that make the myelin sheath (the oligodendrocytes), in contrast to all other known MS treatments, which target immune cells.

There may be other approaches to interfere with the demyelinating process. One area that has received very little attention is the study of proteases (see the chapter by I.A. Scarisbrick). Multiple proteases have been demonstrated in the CNS and have been associated with MS lesions. One specific protease identified at the Mayo Clinic (kallikrein 6) is particularly associated with active demyelination within the MS plaque. Kallikreins are a group of proteases of which the best-known member is prostate-specific antigen (PSA). PSA has become the most important marker of malignancy in clinical practice. Other proteases (and likely kallikreins) may also become specific markers of other disease processes. If these proteases are associated directly with a demyelinating event, then it would be reasonable to design protease inhibitors to target a specific population of enzymes, which could be beneficial in the MS lesion.

Axonal degeneration in MS has been an area of extensive investigation in the last few years (see the chapter by C.L. Howe on axonal pathology). It was once thought that axons were relatively preserved in MS lesions. However, loss of axons has been demonstrated in both acute and chronic plaques, since 20%-30% of axons may be lost within the lesion. Clinical deficits, especially long-term disability, best correlate with the degree of axonal loss. Therefore, understanding the mechanisms of axonal pathology in MS is important. It is possible that demyelination in itself results in axonal pathology. This is supported by the concept that oligodendrocytes provide nutritive factors to axons. Without these factors, axons would then degenerate. The other possibility is that an active immune-mediated mechanism destroys axons. Here again, $CD8^+$ T cells are the most likely culprit. Data both from experimental animals and human disease demonstrate a close association between the number of $CD8^+$ T cells and the degree of axonal pathology. In experimental animals, deletion of the $CD8^+$ T cells, either by genetic knockouts or with antibody treatment directed to these cells, results in improved function with preservation of axons. In addition, a large number of neuroprotective strategies may be applicable to the MS lesion. Traditionally, these strategies have been considered important in diseases such as stroke, where there is ischemia or anoxia. Recent evidence indicates that some of the same factors upregulated in ischemia may also be upregulated in the MS lesion (see the chapter by C.F. Lucchinetti). This suggests that similar neuroprotective factors may be utilized for treatment in MS.

The area of genetics has received wide attention in the last 20 years. MS traditionally is not considered a genetic disease, although there is an increase in concordance in identical twins in MS compared to fraternal twins. However, this concordance is only between 20% and 25%. While this indicates a genetic component, clearly environmental factors account for most of the variance. In an effort to understand the important genetic factors in MS, many large genome studies have been performed (see the chapter by J.P. McElroy and J. Oksenberg). To date, the only genetic factor consistently demonstrated to be associated with MS is HLA, specifically the DR2 haplotype associated with $CD4^+$ T cells; this has been consistently observed in most subsets of MS patients. This genetic factor, however, only explains a very small percentage of the genetic variance of MS. Clearly, other genes also play a role. Unfortunately, large genome studies have failed to identify these

genes, and it is possible that the difficulty has been in grouping all MS patients together. If the neuropathological observations hold true, there may be specific subtypes of MS. It may be necessary to perform genetic studies segregating the various subtypes of MS to see if associations are stronger. The pathological substrates (see the chapter by C.F. Lucchinetti) are very distinct in that they either target the myelin sheaths or the oligodendrocytes. It would be reasonable to assume that different genetic factors play a role in each of these various subtypes.

In addition, genetics may also play a role in the degree of spontaneous remyelination occurring in MS (see the chapter by A.J. Bieber). Some genetic strains in experimental models spontaneously remyelinate following a demyelinating incident, but others do not. Mating studies between these strains have shown the remyelinating components to be dominant, such that remyelination is expressed as a dominant trait. Similar events may occur in MS lesions. Some patients spontaneously remyelinate following MS attacks and recover completely following acute events. In contrast, other patients develop an acute attack from which they never fully recover; these patients are less likely to exhibit full remyelination. No genetic studies in MS thus far have compared patients who remyelinate (recover completely from MS attack) to those who do not remyelinate (fail to recover from acute attacks). Genetic studies of the experimental models may provide unique insights on how to study the genetics of MS.

To develop successful treatments for remyelination, we will need specific surrogates of remyelination to follow in clinical trials. The most obvious surrogate for studying remyelination is magnetic resonance imaging (MRI) (see the chapter by B.J. Erickson and the chapter by I. Pirko and A.J. Johnson). Preliminary data in experimental animals suggest an association between remyelination and decreased size of T1 and T2 lesions. In addition, magnetic transfer may be a reliable measure and surrogate marker for remyelination. These observations will require detailed study in experimental animals before they can be applied to clinical trials in MS. However, given that treatment approaches for remyelination may soon reach the clinical arena, it becomes essential to develop MRI technologies to distinguish between remyelinated and non-remyelinated lesions.

Further studies in the epidemiology of MS may help determine the pathogenesis of the disease or may give a link to treatment. This has been the case in the investigation of the link between uric acid and demyelination (see the chapter by S. Spitsin and H. Koprowski). Epidemiological studies have shown that patients with high uric acid are less likely to develop MS, whereas MS tends to be associated with lower levels of uric acid. Whether this observation can be converted into a clinical treatment paradigm remains to be determined. Similarly, the statin drugs commonly used for the treatment of lipid metabolism disorders are gaining significant interest for the treatment of MS. These statin drugs may have an effect on the immune system that may be beneficial in MS. Some experimental studies using these statin drugs are in process, while others are under consideration. Of concern is the statin drugs' effect on lipid metabolism, since myelin itself is a lipid membrane. It is unknown whether statins in themselves are detrimental from the standpoint of oligodendrocyte function. It will be important to determine whether the use of statin

drugs is associated with different clinical outcomes in MS. The issue is complex because there may be both beneficial and harmful effects of statins. Statins may be beneficial in downregulating the immune system; however, statins may also be harmful to lipid membranes causing injury to the oligodendrocyte (see the chapter by M.S. Weber and S.S. Zamvil).

Similarly, based on the observation that MS improves during pregnancy, there is growing interest in using hormone therapy in MS (see the chapter by E.A. Shuster). Again, hormones such as estrogen and progesterone may positively affect the immune system while potentially harming myelin/oligodendrocyte biology.

Finally, we hope that the reader will appreciate the diversity of approaches needed to understand the pathogenesis of this most disabling disease. Only by discarding the paradigm that the inflammatory response is the causative factor of MS will we make significant headway in the treatment of this disease. Clearly, inflammatory response influences pathogenesis; however, whether it is the primary contributor to the demyelinating disease process or whether it is primarily a response to an exogenous factor and therefore, playing a reparative role, still remains undetermined. The work of the talented investigators contributing to the various chapters of this book provides great hope for our patients with MS. These investigators are dedicated to finding a cure and ultimately eliminating this disease completely from the textbook of neurological diseases. One cannot help but draw analogies to human poliomyelitis. During polio outbreaks, hundreds of patients were hospitalized and required respiratory support with the use of iron lungs. The dedicated efforts of investigators, scientists, epidemiologists, virologists, immunologists and clinicians identified a single causative agent that induced poliomyelitis. Development of a vaccine for polio has led to the near disappearance of poliomyelitis in most parts of the world. We work toward a similar scenario in our lifetime with MS.

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