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Are current immunological concepts of multiple sclerosis reflected by the immunopathology of its lesions?

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Abstract. Immunopathological studies on multiple sclerosis (MS) brain clearly indicate that a T cell-mediated immune response is the driving force in the induction of the lesions. This T cell-mediated response alone, however, is not sufficient to explain the widespread and selective destruction of myelin sheaths. According to present evidence, it is likely that antibodies directed against surface components of myelin sheaths are at least one factor involved in the demyelinating process. The patterns of inflammation, demyelination and oligodendrocyte destruction, however, suggest that the pathogenesis of the lesions may be fundamentally different in individual MS patients and that autoimmunity may not be the sole cause. In the case of autoimmune reactions various different proteins of the nervous system may become targets and it appears unlikely, that myelin basic protein is a major candidate for a pathogenetic role in MS.

Introduction

The pathology of multiple sclerosis (MS) was defined more than a hundred years ago [3, 6, 29]. The disease is characterized by plaques of demyelination and sclerosis, randomly distributed throughout the central nervous system (CNS). The nature of these lesions is thought to be selective, involving mainly myelin and its supporting cells, the oligodendrocytes, but sparing other tissue elements of the nervous system, such as axons, neurons or astrocytes. During active disease, demyelination is associated with an inflammatory reaction, which is predominantly accomplished by lymphocytes and macrophages. It is generally believed, although not formally proven, that the chronic inflammatory process in the nervous system is responsible for the destruction of myelin sheaths. Infectious agents have not been reproducibly isolated from MS lesions and immunosuppression has a significant beneficial effect on the development

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of the disease. Furthermore, autosensitization in humans may lead to a disease which, at least on the basis of the pathology of its lesions, is indistinguishable from MS [47, 57].

For these reasons MS is believed to be an autoimmune disease, triggered in genetically susceptible individuals by an exogenous factor, possibly a virus infection during childhood. However, the nature of the autoantigen, and the mechanism by which the immune system exerts its deleterious effects on the nervous system, are still subjects of controversy. In the present review, recent observations on the immunopathology of MS will be summarized and critically discussed in the light of current immunopathogenetic concepts of the disease.

Immunopathology of brain inflammation in MS

The inflammatory reaction in MS is dominated by lymphocytes and macrophages. More detailed characterization of lymphocytes in MS lesions revealed controversial data on the relative numbers of $CD4^+$ and $CD8^+$ cells and their subsets [9, 12, 53]. This, however, is not surprising due to the extensive recruitment of secondary, antigen-nonspecific inflammatory cells into established inflammatory foci [5, 51]. Yet the bulk of evidence suggests that in early active lesions $CD4^+$ cells of the "helper/inducer" phenotype dominate, whereas there may be a significantly lower incidence of $CD45R^+$ putative "suppressor/inducer" cells compared to other inflammatory diseases of the CNS [12, 53]. T cell receptor analysis suggests oligoclonal expansion of both α/β [33] and γ/δ T lymphocytes [63] within MS lesions.

Although much fewer in numbers, B lymphocytes and plasma cells contribute to the inflammatory reaction [8, 32]. Interestingly, the relative frequency of immunoglobulin-producing B cells and plasma cells is significantly higher in the lesions of MS patients in the late chronic stage of the disease, compared to lesions formed in Marburg's type of acute MS or during the first or second bout of chronic MS [22, 35]. A considerable proportion of plasma cells within chronic MS lesions have been shown to locally produce antibodies against myelin basic protein (MBP) [11].

The dominant leukocyte population in MS lesions are macrophages. Macrophage activation and phagocytosis of myelin proteins in the lesions are reliable indicators of ongoing demyelinating activity [18, 23, 35, 46].

The inflammatory reaction in MS brains is associated with the up-regulation of immune-associated molecules and cytokines on infiltrating leukocytes as well as on resident cells of the nervous system. As an example, activated endothelial cells in active lesions may express adhesion molecules [7, 54], fibronectin [52], urokinase plasmin activator receptor [7], major histocompatibility complex molecules [7, 55], and stress proteins, and may be dressed with activated complement [4]. Undoubtedly, these molecules are important for the passage of inflammatory cells through the blood-brain-barrier.

Data on the expression of cytokines in MS lesions are incomplete and controversial. By polymerase chain reaction (PCR) amplification interleukin (IL)-1 mRNA has consistently been found in active lesions [64], whereas mRNAs for IL-2, IL-4 and IL-10 were present only in a small minority of plaques or completely absent [43, 64]. In addition, mRNAs for certain intercrines (IL-8 and membrane cofactor protein) were detected. In situ hybridization revealed mRNAs for a variety of cytokines [IL-1, 2, 4, 6 10, interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α) and

transforming growth factor (TGF)-β1 and 2] exclusively expressed in perivascular inflammatory cells [62]. On the other hand, immunocytochemistry demonstrated a reactivity for IL-1, IL-2 and lymphotoxin in inflammatory cells and for TNF-α and IFN in macrophages and astrocytes [13, 50, 56]. For technical reasons that reside in the poor suitability of anti-cytokine antibodies for immunocytochemistry as well as in problems of sensitivity of the in-situ hybridization techniques, the significance of these results is at present difficult to assess.

A major aspect of the discussion on the immunopathology of MS is, that all the above-described features are not specific for this disease, but can be found, with some variation due to the stage or the etiological background, in other inflammatory diseases of the nervous system, in particular in chronic virus infections [14, 31, 54]. Furthermore, similar studies performed in the well-defined models of autoimmune encephalomyelitis do not, in the absence of other experimental evidence, allow major conclusions on the immunopathogenesis of the disease. Thus, from all these results, it is safe to conclude that a T cell-mediated immune reaction, with secondary macrophage activation, is the driving force in the pathogenesis of the lesions and that locally produced antibodies may also be involved in the chronic stage (Fig. 1). However, all further reaching concepts on the immunopathogenesis of the lesions depend upon analogies to well-defined animal models rather than on hard data on the disease itself.

Demyelination and oligodendrocyte destruction

Besides inflammation, demyelination is the second most characteristic feature of MS pathology. As already proposed, at the beginning of this century [29], the demyelinating process is relatively selective, due to segmental destruction of myelin sheaths with sparing of axons. However, emphasis has to be placed on the term "relative", since a variable extent of axonal destruction is present in all demyelinated MS plaque, that, in extreme situations – especially in acute MS –, may affect up to 80% of the axonal population.

Myelin sheaths are destroyed at any location along their internode in a process that has been described as "melting away the myelin" along intact axonal profiles [29]. Macrophages are intimately engaged in the demyelinating process. They are closely attached to acutely demyelinating fibers, and sometimes an interaction between the coated pits and vesicles of macrophages and degenerating myelin sheaths can be seen [36]. In addition, invasion by macrophages and their cell processes of the widened periaxonal space and between myelin lamellae can sometimes be found [18, 37]. Myelin is further dissected into small fragments that are taken up and further degraded by macrophages.

Oligodendrocytes, the cells responsible for formation and maintenance of myelin sheaths, are lost to a large degree, or even completely, in most cases of typical chronic MS [18, 28, 36, 42]. However, in some cases, especially in early stages of the disease, a considerable number of oligodendrocytes may be present in the lesions, and remyelination in these cases may be rapid and complete [1, 18, 35, 38–41]. This raises the question of whether oligodendrocytes are preserved during the demyelinating process or destroyed and newly recruited from undifferentiated precursor cells.

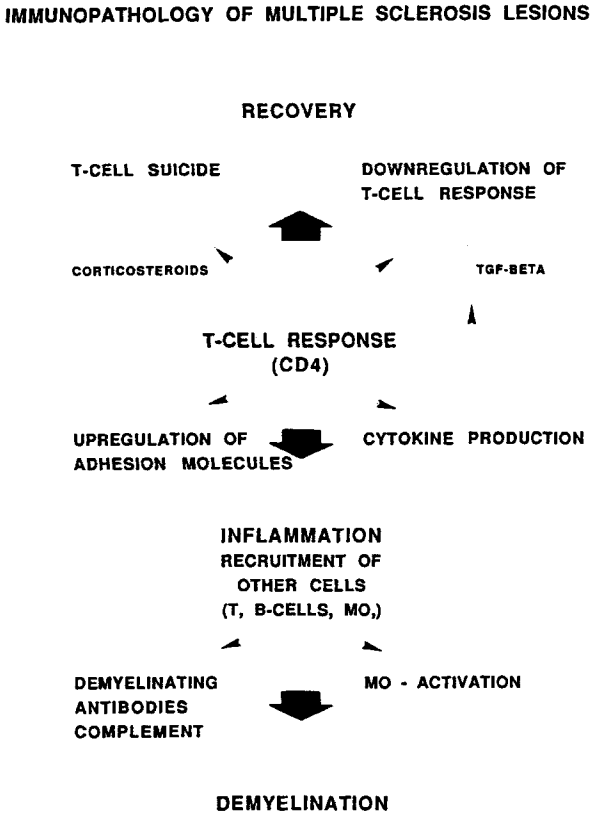

Fig. 1

Recently to address the problem of oligodendrocyte pathology in MS we used new techniques that allowed the positive identification of oligodendrocytes in the lesions and to differentiate between mature oligodendrocytes and precursor cells. In the majority of MS cases of typical long duration (3–20 years), oligodendrocytes were acutely destroyed during active demyelination and completely lost in the demyelinated plaques [22, 35]. However, in biopsy samples obtained during the first or second bout of the disease, oligodendrocytes survived the acute demyelinating episode, and remyelination was rapid and complete [1, 35]. In addition, we found evidence that in some cases of chronic MS oligodendrocyte destruction was secondary to demyelination, whereas in others a primary oligodendrocyte destruction led to secondary demyelination [35]. These data indicate a heterogeneity of the mechanisms that lead to demyelination in different cases and, in a single case, even in early and late stages of disease development.

What immunological mechanisms could be responsible for these patterns of demyelination and oligodendrocyte destruction (Table 1)? For immunologists, the favorite explanation would be that the T lymphocytes responsible for the induction of brain inflammation simultaneously mediate the demyelinating process. However, at present, only few models of pure T cell-mediated acute CNS inflammation lead to

Table 1. Mechanisms of demyelination in inflammatory demyelinating diseases

Mechanism in vitro	Evidence in MS
Virus-induced degeneration of oligodendrocytes	Few cases with primary oligodendrocyte destruction [35]
T cell cytotoxicity (γ/δ T cells)	Abundance of γ/δ T cells in some cases [49]
Demyelinating antibodies	Intrathecal synthesis of anti-MOG antibodies [34], receptor-mediated phagocytosis of myelin [36]
Bystander damage of myelin (enzymes, reactive oxygen species, nitric oxide, TNF-α)	Abundance of activated macrophages in lesions [23]
Complement-mediated lysis of myelin and oligodendrocytes	Presence of immunoglobulins and complement in lesions [4]

MS, Multiple sclerosis; MOG, myelin oligodendrocyte glycoprotein; TNF, tumor necrosis factor

significant demyelination [18, 21]. When more significant demyelination is present in putatively pure T cell models of CNS inflammation, it is found exclusively in chronic variants, where involvement of other, additional immunological mechanisms has not been excluded. In vitro, oligodendrocytes can be destroyed by TNF-α [48], complement or perforin [44, 45]. However, in vivo effects are minor [2] and possibly counteracted by other cytokines [27].

Another mechanism that has been suspected of being involved in demyelination is cytotoxicity of γ/δ T lymphocytes against oligodendrocytes that express the stress protein hsp65. In vitro, oligodendrocytes can be preferentially lysed by γ/δ T lymphocytes [10] and a co-localization of γ/δ T lymphocytes with oligodendrocytes that express hsp65 hase been described in MS lesions [49]. Clonal expansion of γ/δ cells within MS plaques [63] further argues in favor of their pathogenetic role in the disease. Yet, the essential questions on the role of γ/δ T cells in MS are still unresolved. It is not clear which antigen is recognized by γ/δ T cells within MS lesions and whether heat-shock proteins are involved at all. No experimental evidence is available which shows that γ/δ T lymphocytes home to the CNS after transfer and lyse oligodendrocytes in vivo. Heat-shock proteins, including hsp 65, in MS lesions are not restricted to oligodendrocytes, nor is infiltration by γ/δ T lymphocytes restricted to lesions with oligodendroglia destruction ([63] and Lassmann, unpublished). Finally, studies up to now have failed to show any evidence that oligodendrocytes degenerate in MS lesions in the course of contact with γ/δ T lymphocytes.

Extensive demyelination can be induced in vivo in models of autoimmune encephalomyelitis when, in addition to the encephalitogenic T cell response, antibodies against surface components of the myelin sheaths are present [19, 24, 25]. Indeed, several observations indicate that in MS patients such demyelinating antibodies may be involved in the pathogenesis of demyelination in the lesions. In chronic MS lesions a significant proportion of inflammatory cells in the lesions are B lymphocytes or plasma cells. B cells and plasma cells that produce antibodies against myelin oligodendrocyte glycoprotein (MOG) can be found in the CSF of chronic MS patients [34]. Since MOG is expressed on the surface of human myelin sheaths, local production of antibodies against this antigen is a potential risk for myelin sheaths when activated effector cells are present in the course of T cell-mediated brain inflammation [20, 25]. The interaction of myelin with coated pits of macrophages during demyelination indicates a receptor-mediated endocytosis of myelin, possibly through antibody opsonization [36]. On the other hand, to date no consistent pattern of anti-MOG or

demyelinating antibodies has been found in serum and CSF of MS patients. Absence from the CSF is not surprising, since such antibodies, directed against antigens on the surface of myelin, have to be absorbed by the adjacent myelinated CNS tissue. Furthermore, it is not yet clear whether MOG is the only immunodominant myelin surface antigen in the induction of demyelinating antibodies.

It has to be emphasized that in our study on demyelination and oligodendroglia destruction in MS, the patterns were variable from case to case. The spectrum ranged from selective destruction of myelin with almost complete preservation of oligodendrocytes to substantial destruction of oligodendrocytes in the course of demyelination and even to primary oligodendroglia destruction with secondary demyelination [35]. These data suggest that the pathogenetic mechanisms leading to demyelination may be fundamentally different in different MS patients.

Lesional topography as a clue to identify target autoantigens in MS

MS, at least in its chronic variants is a disease that affects the CNS, but not the peripheral nervous system. Although inflammatory demyelination of peripheral nerves is a typical feature of Marburg's type of acute MS [29], its incidence in chronic MS is very low [15]. MS lesions may appear in any region of the CNS, yet certain areas of the brain are more frequently affected than others. The highest numbers of lesions are found either in the periventricular white matter or in the periphery of cerebral gyri, in the latter case being either contiguous to or wholly located within the gray matter [28]. Other regions with high density of lesions are the optic nerve and chiasm, pons, cerebellar peduncles, medulla oblongata and spinal cord. However, in early stages of MS different variants exist, predominantly affecting either the spinal cord (myelitis), the optic system (optic neuritis) or the periventricular white matter. In addition, in some MS patients inflammation can be found in the retina and in the uvea, in regions where myelin is absent [30].

This pattern of lesional distribution is in contrast to that found in experimental models induced by autoimmunity against MBP. In these models, CNS lesions are concentrated in the spinal cord and brain stem with very little affection of the periventricular white matter and other forebrain regions [17]. In addition, MBP-induced experimental autoimmune encephalomyelitits (EAE) is associated with inflammatory lesions in the peripheral nervous system, a feature that is rarely encountered in chronic MS [26]. Thus, it is unlikely that MBP is the major target antigen for pathogenic autoimmune reactions in MS.

However, other CNS antigens have been identified that could be targets of a T cell-mediated autoimmune encephalitis. They include proteolipid protein (PLP) [58], MOG [26], myelin-associated glycoprotein (MAG) [59], S-100 protein [17] and glia fibrillary acidic protein (GFAP) (Linington unpublished). The topography of lesions, induced by T cell reactions against these various nervous system antigens is quite variable. Obviously, inflammation is restricted to the CNS, when the T cells recognize an antigen, such as MOG or PLP, that is exclusively present there. When antigens are recognized that are present in the compact myelin, such as MBP or PLP, the highest incidence of lesions is present in areas with the thickest myelin sheaths: the spinal cord and the brain stem. Conversely, an antigen exclusively localized on the myelin surface e.g. MOG, is present in high concentrations in areas with many thin myelin sheaths. Thus, inflammation after transfer of MOG-reactive T cells severely affects the

Table 2. Target antigens for autoimmunity in the nervous system

Antigen	Histological localization	Topography of inflammatory lesions in experimental animals		Postulated human disease
MBP	Central myelin	Spinal cord	+++	Myelitis
	Compact myelin	Medulla	++	Neuromyelitis optica
		Optic nerve	+	
		Periventr.	+	
	Peripheral myelin	PNS	+	PNS involvement in acute MS
PLP	Central myelin	Spinal cord	+++	Myelitis
	Compact myelin	Medulla	++	Neuromyelitis optica
		Optic nerve	+	
		Periventr.	+	
MOG	Central myelin	Spinal cord	++	Classical chronic MS
	Myelin surface	Medulla	++	
		Optic nerve	+++	
		Cerebellum	+++	
		Periventr.	+++	
S100	Astrocytes	Spinal cord	+++	Chronic MS with eye involvement
	Eye	Medulla	++	
		Optic nerve	+	
		Cerebellum	+	
		Periventr.	+	
		Cortex	++	
		Retina	++	
		Uvea	++	
	Peripheral nerve	PNS	+	PNS involvement

MBP, Myelin basic protein; PLP, proteolipid protein; MOG; myelin oligodendrocyte glycoprotein; S100, S-100 protein; PNS, peripheral nervous system

brain, including the periventricular and cerebellar white matter. Inflammation induced by T cells against an astrocytic antigen, such as S-100 protein, in addition to the typical white matter lesions, also leads to severe involvement of the cerebral cortex, the retina and the uvea.

When the patterns of lesional topography are compared between the models of autoimmune encephalitis and MS, it is evident that MBP is in the vast majority of MS cases not a suitable candidate for a pathogenic autoimmune response. In the future it will have to be determined whether different forms of MS – pure spinal forms, neuromyelitis optica, cases with dominant periventricular involvement, cases with severe eye involvement – reflect dominant autoimmune reactions against different CNS components (Table 2). In addition, it has to be considered that the inflammatory reaction in MS may be induced or propagated by simultaneous immune reactions against a variety of different autoantigens [34]. In this case the final pathological outcome and lesional distribution has to depend upon the aggregate of the individual autoimmune responses.

In conclusion, the review of the immunopathology of MS suggests that the common denominator in its pathogenesis is a chronic immune reaction against one or more antigen(s) presented within the CNS compartment to peripherally predetermined T lymphocytes. A number of different autoantigens and foreign antigens, the latter present in the CNS in the course of latent non-cytopathic infections, may be the primary target of the immune response. With the chronicity of the disease, it is likely that the immune response broadens by recruiting additional autoimmune reactions. The

pronounced and selective demyelination apparently requires immunological mechanisms in addition to the primary T cell response. One of these mechanisms appears to be the cooperation of antibodies in the pathogenesis of demyelination.

Consequence for diagnosis and therapy of MS

From the present experimental evidence, the question arises whether MS is a neurological syndrome with different immunopathological mechanisms triggering a final common pathway rather than a single disease. This may also explain the highly variable clinical course of MS [61] and raises major problems for the evaluation of new therapeutic strategies. The present state of the art is to perform large scale randomized double-blind clinical studies. These studies may be able to measure the efficacy of global immune suppression or detect an interference with a final immunopathological pathway. Yet they often do not reflect the fact that a therapy that is useful in the early stage of MS may be ineffective or even deleterious at later stages. In addition, the usefulness of more delicate therapeutic interventions, such as antigen-specific or immunomodulatory treatments, is probably difficult to prove by these methods.

Most antigen-specific therapeutic trials are based on the assumption that MBP is the immunodominant T cell antigen in MS. However, other candidates, such as MOG [16] or, in some instances, S-100 protein, may be more important, and additional new immunodominant encephalitogenic antigens will certainly be identified in the near future. Furthermore, individual MS patients may react to more than one epitope of known autoantigens. As long as we have no means of pinpointing the responsible encephalitogenic antigen(s) or even the responsible epitope(s) for a given individual MS patient, antigen-specific therapy is unlikely to be a successful option in this disease.

A recently published strategy for antigen-specific therapy is the paradigm of oral tolerization [60]. This is believed to transfer an antigen-specific Th1 response (which is known to induce T cell-mediated encephalitis) to a Th2 response. T cells of the Th2 type produce cytokines that drive mainly B cells and stimulate antibody production. Thus, oral tolerization may be effective in a stage of the disease in which T cell-mediated delayed-type hypersenstitivity is prominent, but in stages or patients with abundance of demyelinating antibodies, such a therapy could be deleterious for the outcome. At least in EAE a delicate interplay between low numbers of encephalitogenic T cells and demyelinating antibodies results in severe disease of the animals with widespread demyelinating lesions [20].

Thus, our growing knowledge of the multitude of different immunological mechanism, that can lead to inflammatory demyelinating lesions in the nervous system, encourages the development of techniques that allow their identification in individual MS patients. This should lead to therapeutic trials in specified subgroups of MS patients with exactly defined uniform patterns and stages of disease.

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