New Immunopathologic Insights into Multiple Sclerosis

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Multiple sclerosis (MS) is a chronic inflammatory and demyelinating disease of the central nervous system. Although the immune system seems to play an important role in the pathogenesis of disease, target antigens are still uncertain and pathways leading to tissue destruction have not been fully elucidated. Recent studies have significantly contributed to a better understanding of the disease process and broadened our view on possible scenarios of disease initiation and progression. We review the role of the immune system for the manifestation and evolution of MS and discuss different pathogenetic concepts. We conclude with an outlook on future strategies to identify the cause of MS.

Introduction

Multiple sclerosis (MS) is the most common chronic inflammatory disease of the nervous system [1,2]. The disease exclusively involves the central nervous system (CNS) and is not associated with any other disorder. MS affects 0.05% to 0.15% of white populations, leading over time to severe disability in half of them. MS occurs twice as often in women as men, and usually starts between the ages of 20 and 40 years. In the majority of patients, the disease course is characterized by onset and remission of neurologic symptoms originating from different areas in the CNS (relapsing remitting [RR-MS]).Over time, the number of relapses decreases, but most patients develop progressive neurologic deficits that occur independently of acute bouts (secondary progressive MS [SP-MS]) and produce significant disability. In 10% to 20% of patients, the disease runs a primary progressive (PP) course from onset without superimposed relapses. SP-MS and PP-MS share several clinical features, including a similar extent and speed of progression [3]. Differences between RR-MS and both forms of progressive MS are also evident on magnetic resonance imaging (MRI) of the brain and spinal cord. In patients with RR-MS, acute CNS lesions followed by spontaneous resolution are frequently observed, even during clinically silent periods. Lesions are mostly located in the white matter and often characterized by disturbance of the blood-brain barrier, local edema, and demyelination reflecting acute inflammation. When evolving into the SP phase and in patients with PP-MS, inflammatory changes are less pronounced but global atrophy develops, which seems to correlate with disability [4,5]. These findings suggest the existence of two distinct disease phases in MS: 1) an initial stage (RR-MS) characterized by recurrent episodes of acute CNS inflammation focused on the white matter; and 2) a progressive stage characterized by predominant neurodegeneration with decreasing inflammation. The second phase may be preceded by the inflammatory phase, but may also unfold independently (PP-MS).

Risk Factors

Both genetic and environmental factors influence susceptibility and the course of MS. The prevalence of MS varies strongly, depending on the genetic background [6]. Prevalence is high in whites, but MS is rare in Asians and Africans. Family members of MS patients are at greater risk, which ranges from 250-fold higher in monozygotic twins to 10-fold higher in children of MS patients [2,7]. In contrast, the prevalence in spouses and adopted children is not increased. Multiple genome screens and family studies recently completed indicate that MS follows a polygenetic trait, which involves a large number of genes with each contributing little to the overall risk [2,7,8]. Furthermore, the studies also provide evidence for significant heterogeneity of susceptibility genes. The role of genetic factors is even more complex because they appear also to impact on disease course. As a result of the polygenetic and heterogeneous genetic predisposition, positional cloning and candidate gene approaches have been largely unsuccessful or yielded inconclusive results [8]. Only the human leukocyte antigen (HLA) class II alleles DRB1*1501 and HLA-DQB1*0601 have consistently been associated with MS in whites (relative risk of 2 to 4) [9]. Although this association was established more than 20 years ago, it is still unknown how these HLA alleles confer greater susceptibility of contracting MS.

Beside the genetic influence, epidemiologic and migration studies have provided circumstantial evidence for an environmental (and possibly transmissible) factor in the pathogenesis of MS [6]. Relapses are associated with common viral infections [10]. The risk of developing MS is highest in areas with a moderate climate. Migration from high-risk to low-risk areas before adolescence reduces risk of developing MS, whereas migration from low-risk to high-risk areas increases the risk of developing MS [11]. The impact of environmental factors is also underlined by a few MS "epidemics," such as the one on the Faroe Islands. On these islands, MS was unknown until British soldiers landed in 1940. Within 3 years a high incidence of MS cases was observed and since then the disease occurs on a regular basis on the Faroe Islands [12].

Pathology of Multiple Sclerosis Lesions

Multiple sclerosis is a disease that predominantly, although not exclusively, affects CNS white matter and leads to demyelinating lesions [13]. Most lesions are located around the ventricles with relation to small vessels. In acute MS lesions, demyelination of axons, activation of microglia, and infiltration of immune cells are key features. The infiltrates mostly consist of T cells and macrophages. B cells and plasma cells are also found, but at lower numbers. Extensive antibody deposition is seen in part of the patients. Eosinophilic granulocytes are sometimes encountered, but other immune cells, such as granulocytes, γ/δ T cells or natural killer T cells, are largely absent from lesions. Among T cells, CD8+ T cells outnumber CD4+ T cells in the parenchyma, whereas the later ones are found more frequently in cuffs and meninges [14,15]. An array of different lymphokines, chemokines, and proteases is expressed in acute MS lesions [16–18].

Work performed by Lucchinetti *et al.* [19] suggests that acute demyelinating lesions significantly differ in terms of oligodendrocyte pathology, the presence or absence of inflammatory and demyelinative changes, and the extent of remyelination. Two patterns have been noted most frequently, one characterized by significant antibody deposits and remyelination, the other by oligodendrocyte loss without remyelination. A high degree of heterogeneity is also demonstrated on the cerebrospinal fluid (CSF) cytology of MS patients. Although in particular the extent of the humoral immune response appears to be stable over time in MS patients, it varies significantly inter-individually [20]. Together with the high variability of the clinical phenotype and in disease progression, it is tempting to speculate whether different pathogenetic pathways and even etiologies underlie those histologically defined subtypes.

MS is, however, not only characterized by its inflammatory, but also by its neurodegenerative changes, which are already prominent early in the course of disease [21–23]. In acute lesions, the extent of axonal damage correlates with inflammation, especially invasion by macrophages and CD8+ T cells, suggesting that both cell populations are directly involved in causing axonal loss [23].

Much less is known about the immunopathology of the chronic active or silent lesions. Chronic active lesions feature ongoing inflammation, demyelination, and axonal degeneration, although inflammation is usually less vigorous than in acute lesions. Gliosis and permanent neuronal and oligodendroglial damage with variable degrees of demyelination occur in the silent lesions with little cellular infiltrates and activation of immune mediators [13,24].

The Classic Experimental Autoimmune Encephalomyelitis Concept

A role of the immune system in the pathogenesis of MS was first suggested by observations of acute demyelinating episodes that followed rabies vaccination. The vaccine was contaminated with myelin antigens, raising the possibility that the disease was induced by an antimyelin immune response. This hypothesis was confirmed in animal models. Immunization with myelin antigens and Freund's adjuvant gives rise to CNS inflammation in susceptible animals. This animal model was termed experimental autoimmune encephalomyelitis (EAE) [25]. Target antigens, extent of demyelination, presence and degree of inflammation, and disease course are dependent on the animal strain and genetic background [26]. The role of an autoimmune response in this model was confirmed by adoptive transfer experiments, which demonstrated that predominantly CD4+ T cells from diseased animals can transmit disease to naive animals. CD4+ T cells secreting T-helper (Th) 1 cytokines (*eg,* interferon γ [IFNγ]), tumor necrosis factor β (TNF-β) and interleukin (IL)-2, and the proinflammatory cytokine TNF-α were more potent in transferring disease than other myelin-specific T cells [27]. T cells secreting Th-2 cytokines (IL-4, IL-5, IL-10, and IL-13) conversely seem to protect from or ameliorate EAE [28]. Although T cells are the disease-transferring population, they rely on innate immunity in the CNS. Microglia cells provide the proinflammatory milieu required for efficient T-cell recognition of autoantigens [29]. All together, these findings established EAE as a prototypic autoimmune disorder and created the widely accepted paradigm that a Th-1 T-cell response to myelin antigens is destructive, whereas a Th-2 response is protective [30].

The Autoimmune Hypothesis of Multiple Sclerosis

Based on the observation that administration of the Th-1 cytokine IFNγ exacerbates MS [31], the EAE concept was extrapolated to the human disease (Figs. 1,2). This was fostered by numerous efforts to characterize immune responses to myelin antigens in MS patients. Antibodies against myelin antigens are detected in serum, CSF, and the CNS of MS patients [32,33]. Similarly, CD4+ T cells specific for a variety of myelin antigens are present in the blood of MS patients

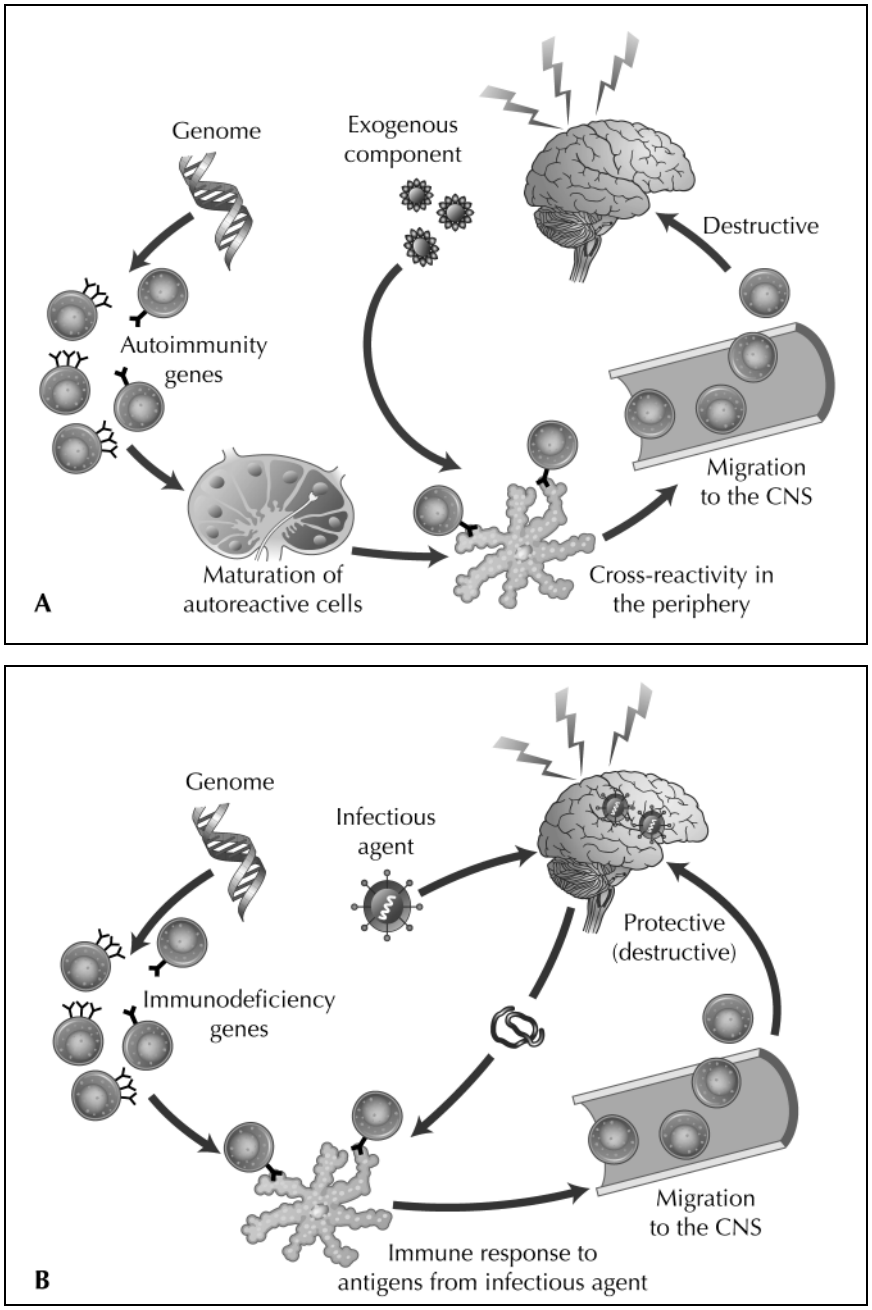

Figure 1. The role of the immune system in multiple sclerosis. The role of the immune system in a possible autoimmune (*panel A*), and infectious (*panel B*), scenario. (CNS—central nervous system.)

[34]. Recent studies demonstrated that these T cells can recognize and respond to a large number of different antigens, among them a variety of self and foreign antigens including peptides derived from microbes [35,36]. However, the ability to react with a large number of different antigens is not confined to autoreactive T cells, but probably an intrinsic feature of T cell recognition [37,38]. Nevertheless, the high degeneracy in T-cell recognition observed provides a possible explanation of how autoreactive T cells may be activated by exogenous infectious agents and initiate a first demyelinating episode (molecular mimicry). After the first destructive event, myelin antigens are released that may further prime a chronic polyreactive autoimmune process (epitope spreading) [39].

Although the autoimmune hypothesis generated in the EAE model involving both molecular mimicry and epitope spreading is attractive to explain many aspects of MS, experimental support for this hypothesis is still limited. Likewise, CD4+ T cells specific for myelin antigens are not only retrievable from MS patients, but also from healthy donors, indicating that autoreactive T cells are part of the normal T-cell repertoire and not necessarily harmful [34]. So far, studies have not provided conclusive results that myelin-specific T cells differ in terms of antigen recognition or phenotype between MS patients and control subjects [34,40]. Similarly, myelin-specific antibodies are not confined to MS, but can be detected in different neurologic diseases and even in healthy control subjects [32,33].

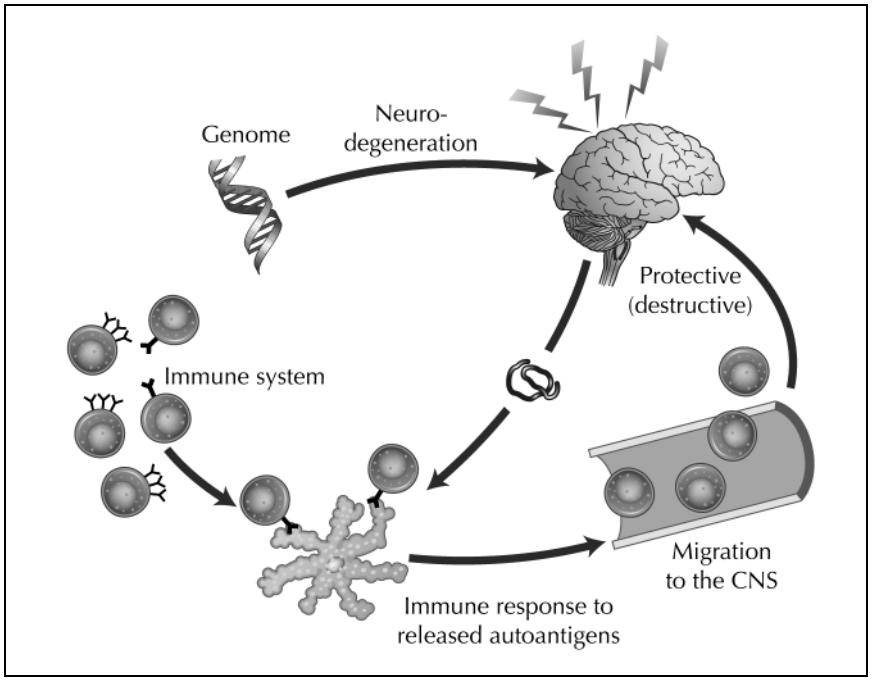

Figure 2. The role of the immune system in a primary neurodegenerative scenario. (CNS—central nervous system.)

Broadening the Autoimmune Concept

During the past decade, many experimental immunotherapies in MS were based on the EAE model. These intervention strategies included global immunosuppression, inhibition of proinflammatory cytokines, or shifting the immune response from Th-1 to Th-2 [30]. However, studies in the EAE model quickly raised questions of whether the Th-1 concept can be applied without modifications to all EAE models and, more importantly, to human disease. The first objections came from studies on genetically modified animals [41]. In some experimental settings, animals lacking IFNγ or TNF-α develop similar or even more severe EAE than their wild-type littermates [41]. In contrast, disruption of the *IL-4* gene does not affect the disease course. In a transgenic mouse model, it was even possible to induce EAE with myelin-specific Th-2 T cells [42]. Finally, a therapeutic approach based on a myelin peptide that induced a Th-2 shift unexpectedly resulted in severe relapses in an EAE monkey model [43].

At variance with the classic EAE dogma, myelin-specific CD8+ T cells may even evoke EAE under certain conditions. In these models, lesions are restricted to the brain and characterized by extensive demyelination and cell death [44•,45•].

Although EAE cannot be adoptively transferred by B cells, antibodies are also undoubtedly important for the disease course. In some models, EAE severity is significantly enhanced by co-administration of myelin-specific antibodies after induction of disease [46].

Clinical trials in MS patients further strengthened the view that the EAE Th-1 concept can not simply be applied to human disease. Treatment of MS patients with a TNF-α blocking antibody or soluble TNF receptor precipitated acute attacks [47]. Global depletion of CD4+ T cells did not have an impact on the disease course of MS [48]. Antigen-based therapies, such as tolerance induction by oral application of myelin or application of altered peptides derived from myelin antigens, were inefficient or even worsened disease [49•,50,51]. Many other immunmodulatory and immunosuppressive drugs failed in clinical trials [51]. To date, only three drugs have been approved for the treatment of RR-MS and SP-MS. Novantrone, a cytotoxic drug with immunosuppressive properties, seems to reduce relapse rates and progression in MS [52]. Glatiramer acetate, a randomly synthesized polypeptide mixture based on four amino acids that are contained at high levels in myelin proteins, also seems to decrease relapse rates [1]. Among the postulated therapeutic effects are its immunomodulatory and neuroprotective properties. So far, the most robust data are available for IFNβ, which strongly suppresses MRI activity, decreases relapse rates, and also seems to affect disease progression [1]. The drug exhibits both antiviral and immunomodulatory effects, although the mode of action in MS is still not entirely understood. Given the inconclusive results on the role of antimyelin responses in MS and the disappointing outcome of a number of clinical trials, a rethinking of the pathogenetic scenarios accumulating in inflammation, demyelination, and destruction of CNS tissue is needed.

Alternative Pathogenetic Scenarios

Inflammation and demyelination are observed not only in autoimmune conditions, but also following infection or even primary neurodegenerative events (Figs. 1,2). The idea that MS is caused by a neurotropic agent has been sup-

ported by the identification of causative viruses in subacute sclerosing panencephalitis (SSPE) or human T-cell leukemia virus-I (HTLV-I)–associated myelopathy [53]. In mammals, a variety of viruses can elicit acute or chronic CNS demyelination and inflammation (*eg*, Theiler's murine encephalomyelitis virus and mouse hepatitis virus) [53,54]. In these models, predominantly CD8+ but also CD4+ T cells are crucial to control the virus in the acute phase [53,54], whereas B cells and antibodies seem to be more relevant during the chronic disease phase [55]. Although T-cell and B-cell responses are clearly important to contain the infection, they may also contribute to tissue damage [56]. The possible negative impact of immune system activation in primary infectious CNS disorders is particularly impressive in experimental Borna virus disease. Untreated animals may develop a severe immune-mediated encephalomyelitis, whereas tolerized or immunosuppressed animals may only develop subtle behavioral abnormalities [57].

Many features of MS are compatible with a chronic CNS infection, but the search for an infectious agent has been utterly unsuccessful. Although many microbes have been associated with disease, up to now evidence is lacking that any of them play a definite role in the pathogenesis of MS. Few pathogens are still the subject of intense investigation as *Chlamydia pneumoniae* and different herpes viruses [58,59].

Inflammation is, however, also seen in acute neurodegenerative disorders, such as traumatic CNS tissue damage and stroke [60,61]. Loss of CNS tissue integrity is associated with microglia activation, cytokine production, and infiltration of leukocytes. The role of the immune system in these disorders is highly variable. Peripheral leukocyte depletion or inhibition of leukocyte migration reduces tissue damage in stroke [62]. In contrast, the induction of a myelin-specific immune response prevents neurodegenereation from some models, such as the axotomy model [63]. Acute neurodegeneration, however, usually does not result in sustained CNS inflammation [61]. Although the early loss of neurons and oligodendrocytes is compatible with a primary neurodegenerative process, the extent of inflammation in MS can only be explained by the involvement of an additional immunologic factor in disease pathogenesis. Possible mechanisms are heightened immunoreactivity to autoantigens or defects in the control of immune responses in the CNS [64].

Concepts involving CNS infection or primary neurodegeneration provide important insights into mechanisms of neuroinflammation, but they have not clarified the etiology of MS. Therefore, recent efforts have focused on the immunologic and neurodegenerative changes in the CNS of MS patients to shed light on the nature of the local immune response. With the emergence of novel techniques, it seems possible to dissect the molecular mechanisms within the CNS and find new clues to disease pathogenesis.

Immunology of the Multiple Sclerosis Lesion

One of the first immunologic observations in MS was the finding of high immunoglobulin G (IgG) levels in the CSF, apparently caused by a local oligoclonal IgG response and mainly entailing IgG1 and IgG3 isotypes [65]. The IgG response involves a limited number of clonotypes being responsible for the oligoclonal IgG banding pattern in CSF. Indeed, the occurrence of an oligoclonal intrathecal antibody response is still the only reliable immunologic test in the diagnosis of MS, although it is not specific and is similarly found in a variety of other predominately infectious diseases of the CNS (*eg*, SSPE, neurosyphilis, neuroborreliosis). In these disorders, the antibodies comprised in the oligoclonal bands recognize antigens from the infectious agents [66]. The pattern of intrathecal antibody production in MS does not change significantly during the course of disease, suggesting that the same antibodies are secreted over a long period of time [67]. These findings were recently complemented by B cell repertoire analyses in CSF and CNS of MS patients [68–71]. All studies demonstrated a preferential use of specific heavy chain genes or clonotypic accumulation of B cells in the local compartment. B cells in the CNS lesions display extensive replacement mutations clustered in the hypervariable region of B-cell receptor (BCR) genes. Comparable BCR maturation is only seen after repeated exposure of memory B cells to the same antigen.

Similar findings have been obtained concerning the T-cell response in the CNS of MS patients. By analyzing single cells from CNS lesions or CSF of MS patients, two groups demonstrated clonal accumulation of T cells in the local compartments. Clonal expansion predominantly of CD8+ and to a much lesser extent of CD4+ T-cell populations was noted [15,72•]. In the lesions of one patient, up to 30% of all T cells were derived from a single CD8+ T cell as evidenced by the analysis of the molecular structure of their rearranged T-cell receptor [15]. These T cells were identified only at low numbers in the blood of these patients, suggesting specific migration to and accumulation in the CNS compartment [72•].

Immunologic Clues to Multiple Sclerosis Etiology

Two main findings characterize the recent advances in our understanding of MS immunology. MS is a heterogeneous disease with respect to clinical phenotype, its pathologic changes, and its inheritance. This level of complexity is contrasted by the highly focused local immune response in the brain of MS patients. A significant number of the T cells in lesions originate from single cells. Similarly, B cells are clonotypically accumulated in the brain of MS patients and their BCRs are antigen maturated.

Although the primary event, which drives the immune response in the CNS, is still unknown, it its highly likely that the initiation and perpetuation takes place in the lym-

phoid tissue [73]. Antigens released from the CNS compartment are processed and presented by antigen-presenting cells. Dendritic cells (DC) probably play a key role in this process, because they can prime both CD4+ and CD8+ T cells. Similarly, B cell responses are initiated when soluble antigens enter spleen and lymph nodes. Specific recognition of the antigens results in clonal expansion of both T and B cells. After acquisition of effector functions, these cells circulate through the body and enter the CNS. The mechanism of transendothelial migration is mediated by the complex interplay of cellular adhesion molecules, chemokines, and matrix metalloproteinases [74]. Within the CNS, they encounter their target antigens presented by CNS cells. CD8+ T cells will respond to antigen presented by HLA-class I–expressing CNS cells, among them neurons and glia cells. Upon recognition of the specific HLA:peptide complex, the cells may release cytokines and directly damage the antigen presenting cells. In vitro, CD8+ T cells can lyse neurons and oligodendrocytes (Fig. 3) [75,76] and induce neurite damage in an antigen-dependent fashion [77]. Given the broad expression of HLA-class I molecules in the brain, the accumulation of CD8+ T cells, and the extent of axonal loss and demyelination in acute lesions [22], it is likely that CD8+ T cells play a central role in the inflammatory process in the CNS of MS patients.

CD4+ T cells require presentation of antigens in the context of HLA-class II molecules. The major source of endogenous HLA-class II expression in the CNS is activated microglia cells. Upon reactivation, CD4+ T cells initiate effector functions and synthesize cytokines and chemokines. The release of proinflammatory molecules recruits other inflammatory cells, such as macrophages, to the lesion (Fig. 3). Although CD4+ T cells play a central role in EAE, their function in MS is less clear. The cells are predominantly found in the meninges and do not seem to be of clonal origin [14,15]. Both findings do not exclude a central role of CD4+ T cells in MS because the capacity of CD8+ T cells to expand clonally is much higher than for their CD4 counterpart [78]. CD4+ T cells could still target defined disease-associated antigens, but in a much broader fashion. On the other hand, CD4+ T cells in the brain of MS patients have the capacity to release neurotropic factors such as brain-derived neurotrophic factor (BDNF) [79]. Thus, it is tempting to speculate that some of these cells are important for neuroregeneration and protection, as observed in the axotomy model [63].

Finally, the humoral immune response also seems to play an essential role in disease pathogenesis. This view is supported by the occurrence of a persistent intrathecal IgG response and the clonal accumulation of B cells in the CNS of MS patients. In contrast with T cells, antibodies are not dependent on presentation or HLA expression and can recognize both soluble and bound proteins. IgG1 antibodies binding to cell surfaces activate the complement cascade and could thus directly damage the antigen-expressing cell (Fig. 3). However, similar to CD4+ T cells, antibodies may not only mediate detrimental effects, but also promote regeneration [80]. According to the animal studies, the humoral immune response seems to be most important in the chronic phase of disease. Several studies have investigated the target of the local humoral immune response in MS. Using expression or phage display libraries, antigen mimics were identified, although as yet their pathogenetic role in MS has not been established [81,82].

Besides the acquired immune response, both macrophages and microglia also seem to be essential for demyelination and axonal loss (Fig. 3) [23]. In the context of active ongoing demyelination, a number of toxic molecules may be generated in an inflammatory cascade: glutamate, nitric oxide, matrix metalloproteinases, calpain, and so forth [60,83]. The vigorous inflammatory response may thereby antigen-nonspecifically inflict damage on the axon. It is widely assumed that the final common pathway is calcium overflow facilitated by up-regulation of N-type calcium channels, consequent calpain activation, and eventually cytoskeleton disintegration. Finally, loss of neurotrophic support may compromise axonal and neuronal survival.

The Focus of the Immune Response

The immune response in the CNS of MS patients during the inflammatory phase of the disease appears to be highly focused, involving CD8+ and CD4+ T cells and B cells. The occurrence of a conserved and persistent intrathecal IgG1 and IgG3 antibody secretion is consistent with an ongoing immune response against proteins. The dominance of a CD8+ T cell response argues that at least part of the target antigens are derived from endogenous proteins that are synthesized within CNS cells. Given the recent broadening of the EAE concept by demonstrating encephalitogenicity of CD8+ T cells, both self antigens and antigens from neurotropic pathogens are possible candidate target antigens in MS. The focus of the immune response to the CNS limits the number of autoantigens to those that are exclusively expressed in the CNS or which occur in a unique modification in the CNS (*eg*, splice-variants). Alternatively, the proteins could be derived from an intracellular pathogen. This pathogen must enter the CNS and persist there without being associated with any life-threatening diseases. Given the worldwide distribution of MS and the fact that significant epidemics have not occurred in areas where MS had been endemic before, such a pathogen must be ubiquitously present. Most of the current candidate pathogens fulfill these requirements.

At this point, it remains uncertain what accounts for the heterogeneity in clinical phenotype and pathology. Theoretically, two scenarios are possible. In case of MS being caused by one defined pathogen/autoantigen, the heterogeneity is most likely a result of the individual genetic mix-up that governs the extent and phenotype of immune responses, vulnerability of the different CNS cells, as well as their neuroprotection and neuroregeneration.

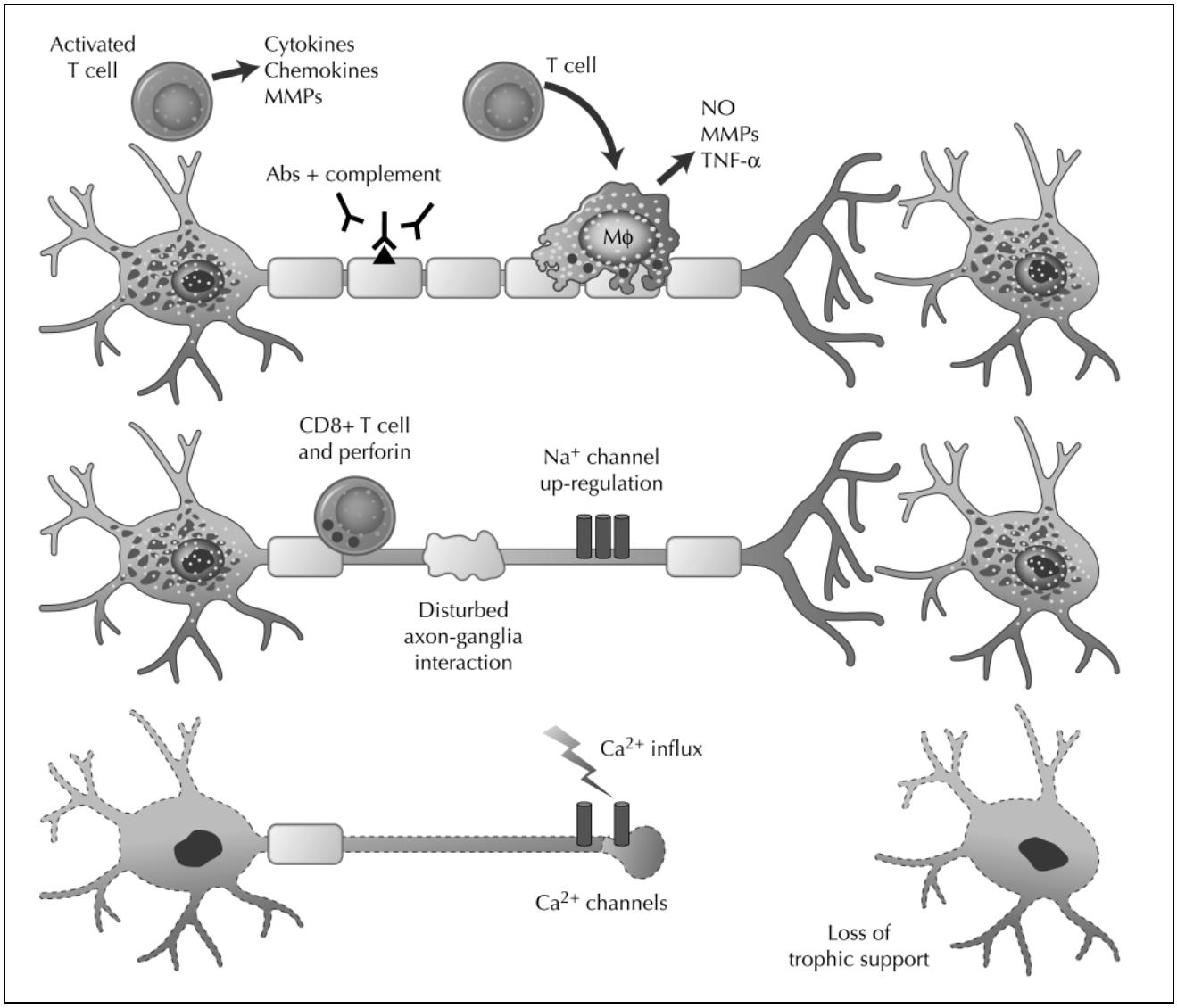

Figure 3. Cascade of events possibly underlying demyelination and axonal degeneration in multiple sclerosis. Within the central nervous system, activated T lymphocytes release inflammatory cytokines, chemokines, and matrix metalloproteinases (MMPs). Moreover, T cells activate microglia cells/macrophages to enhance phagocytic activity, the production of cytokines, and the release of toxic mediators such as nitric oxide (NO), propagating demyelination and axonal loss. Autoantibodies (Abs) crossing the blood-brain barrier or locally produced by B cells or mast cells contribute to this process. Autoantigens activate the complement cascade, resulting in the formation of the membrane-attack complex and subsequent lysis of the target structure. CD8+ cells are capable of attacking the axon and oligodendrocytes directly. The combination of toxic signals and the disturbed axon-glia interaction pave the way for axonal degeneration. The up-regulation of Ca^{2+} channels and the increased Ca^{2+} influx might perpetuate this process. High-frequency signaling of neurons results in axonal degeneration, especially upon exposure to nitric oxide. The loss of signaling activity and trophic support might contribute to axonal degeneration in connected neurons as well. (TNF-α—tumor necrosis factor α.)

Alternatively, the causative pathogen/autoantigen may vary in individual patients, thus being the main driving force for the variability in clinical phenotype and pathology.

Conclusions

The key players in the immunopathology of MS have now been defined. Recent studies suggest that B cells and T cells that clonally accumulate in the lesion are driven by defined protein antigens, independently of whether the response is causative or protective. One of the main goals over the next few years will be to define which antigens attract the acquired immune response to the CNS. Techniques are now available that allow determination of ligands for both antibodies [84] and T cells [85]. For both approaches it will be essential to identify and isolate the relevant antibodies and T cells from the organ compartment. The success of approaches to identify the target antigens will largely depend on tools that incorporate all possible ligands with the naturally occurring modifications. These studies have to be supplemented by the use of new high-throughput techniques that allow dissection of the MS lesions in order to determine the expression profile of

genes and proteins [86,87•,88•]. The success of these approaches will in large part depend on the quality of samples and the rigorous use of appropriate controls to determine which expression pattern is unique to MS and not only related to CNS inflammation. Although we are just at the beginning of these studies, refocusing research on the human disease and the initial events leading to the manifestation of MS may finally provide new insights in the etiology and pathogenesis of MS. We may then have the chance to design and employ therapies that significantly impact on the course of this disabling disease.

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