15 Autoimmune Processes in the Central Nervous System

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Abstract: In this chapter we discuss the factors that contribute to the unique immunological environment of the central nervous system and the mechanisms that may account for the development of autoimmunity within the CNS, including infectious agents as inducers of autoimmune disease. Consideration is given to a variety of human neurological diseases of autoimmune or presumed autoimmune etiology: autism, neuromyelitis optica, neuromyotonia, schizophrenia, lethargic encephalitis and stiff-man syndrome. Also, we discuss autoimmunity as a possible mediator of CNS repair and examples of the protective effects of bacterial and helminth infections on CNS disease. Multiple sclerosis and models of multiple sclerosis are discussed with special attention given to the Theiler's virus-induced demyelination model.

List of Abbreviations: BBB, blood–brain barrier; CNS, The central nervous system; CTL, cytotoxic T cell; CVE, cerebrovascular endothelial cells; DTH, delayed type hypersensitivity; EAE, experimental autoimmune encephalomyelitis; EL, encephalitis lethargica; GAD, glutamic acid decarboxylase; ICAM-1, intracellular adhesion molecule-1; INS, insulin; LFA-1, lymphocyte functional antigen-1; MHC, major histocompatibility complex; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; NMO, Neuromyelitis optica; NMT, neuromyotonia; OCB, Oligoclonal bands; PGE2, Prostaglandin E2; SC, Sydenham's chorea; SCI, Spinal cord injury; TGF-β, transforming growth factor-β; TVID, Theiler's virus-induced demyelination; VAA, vasoactive amine

1   Immunological Reactivity within the Central Nervous System

The central nervous system (CNS) has been considered to be an immunologically privileged site since the early transplantation work of Peter Medawar (Medawar, 1948). Medawar noted that skin transplants survived for longer periods of time in the brain than in other peripheral sites. Antigens injected directly into the CNS parenchyma remain invisible to the immune system but a vigorous delayed-type hypersensitivity (DTH) response may be induced following peripheral antigen administration (Matyszak and Perry, 1995). In contrast, allografts injected into the ventricles are rapidly rejected (Mason et al., 1986). Thus, the immune response in the CNS parenchyma differs considerably from the immune response in other compartments. The reason for diminished immune activity within the CNS is thought to be to avoid immunologically mediated tissue damage that would have devastating consequences on the neurological functioning of the organism. However, the disadvantage of this phenomenon is that the CNS becomes an ideal environment for persistent viral infections.

2   Factors that Contribute to the Immunologically Privileged Status of the CNS

In order to develop an immune response, an antigen is taken up by an antigen-presenting cell, processed, and presented in the context of major histocompatibility complex (MHC) class II to a T cell. The interaction between the costimulatory molecule B7 on the antigen-presenting cell and CD28 on the T cell is also a requirement for T-cell activation. One of the most important factors that contribute to the immunological inactivity of the CNS is the lack of expression of MHC within the CNS.

Other characteristics that were originally thought to be involved in the immunologically privileged status of the CNS are the lack of lymphatic drainage and the paucity of professional antigen-presenting cells within the CNS (Cserr and Knopf, 1992). Additionally, the blood–brain barrier (BBB) was thought to protect the CNS from immunological damage. However, research has now demonstrated that these concepts are incorrect. There is a connection between the brain and cervical lymph nodes and spleen (reviewed in Bradbury and Cserr, 1985). Both microglial cells (Matsumoto et al., 1992) and astrocytes have been shown to function as antigen-presenting cells (Fontana et al., 1984; Borrow and Nash, 1992) and dendritic cells have been detected in the CNS (Greter et al., 2005). In addition, the BBB does not in fact prevent immune cells from entering the CNS and activated T cells continually pass through into the CNS in

surveillance mode (Wekerle et al., 1986; Hickey et al., 1991). Although DTH responses in the brain are suppressed (Harling-Berg et al., 1991; Streilein, 1995), humoral immunity appears to be enhanced (Harling-Berg et al., 1989). Interestingly, the isotype of antibody produced in the CNS appears to be biased toward noncomplement-fixing IgG subclasses. There are also low levels of complement in the CNS that reduces the inflammatory reactions mediated by complement-fixing antibody.

In addition, there appears to be active immunosuppression in the CNS (Brent, 1990), which may be mediated by transforming growth factor-β (TGF-β) (Streilein and Wilbanks, 1992). Constitutive FasL expression within the CNS is also thought to play a role in protecting the CNS from immunological damage. Both astrocytes (Fontana et al., 1982) and microglia (Keane, 1997) release prostaglandin E2 (PGE2) following stimulation with LPS. PGE2 inhibits the proliferation of T cells and also decreases MHC class II expression on macrophages (Keane, 1997). Lipocortins or annexins are calcium- and phospholipid-binding proteins that are induced by glucocorticoids and mediate anti-inflammatory effects (Goulding et al., 1990). Lipocortins 1, 2, 4, and 5 are detected within the CNS (Elderfield et al., 1992) and may also be involved in the anti-inflammatory milieu of the CNS.

3   Loss of Tolerance as a Mechanism of Autoimmunity in the CNS

The thymus plays a key role in the education of T cells and the deletion of T cells that recognize self-proteins. The thymic epithelium has been shown to translate a diverse array of organ-specific antigens, which represent all of the tissues in the body (Derbinski et al., 2005). T cells that recognize these self-determinants are deleted. However, in autoimmune diseases self-reactive T cells clearly escape this purging process and may become pathogenic. Research in the diabetes field has led to a better understanding of the process of tolerance. Members of the insulin (INS) gene family of self-proteins are expressed in the thymic stroma in precise hierarchy and location. IGF2 is expressed at the highest levels in thymic epithelial cells followed by IGF1 in thymic macrophages and INS at the lowest levels in thymic medullary epithelial cells and/or dendritic cells (Geenen and Brilot, 2003). Thus IGF2 is better tolerated than INS. In the biobreeding (BB) rat, an animal model of diabetes, there is a defect in IGF2 expression which is thought to explain the absence of tolerance to INS-secreting β cells in these animals. Investigations of loss of tolerance to myelin in mice have shown that the thymus contains significant amounts DM-20, a proteolipid protein (PLP) isoform in which 35 residues (including the encephalitogenic sequence PLP139–151) have been removed by alternative splicing (Anderson et al., 2000; Klein et al., 2000). Thus failure to delete potentially autoaggressive T cells with specificity for PLP139–151 probably arises through the lack of thymic expression of this self-peptide. However, this mechanism does not apply in the case of myelin oligodendrocyte glycoprotein (MOG)-induced experimental autoimmune encephalomyelitis (EAE). Despite the expression of MOG in the thymus, T cells reactive to MOG fail to be eliminated (Fazilleau et al., 2006). One reason for this may be the fact that MOG is only expressed in the medullary thymic epithelial cells, whereas both myelin basic protein (MBP) and PLP are expressed in this site and also in cortical thymic epithelium (Gotter et al., 2004).

4   Infectious Agents and Autoimmunity within the CNS

Autoimmunity can result following infections with either viruses, bacteria, or parasites. In this section, we review some of these infectious agents.

Autoimmune reactions have been reported in acute and chronic viral infections both with RNA and DNA viruses in animals and in man (Notkins et al., 1984). Autoantibodies produced during these viral infections are usually of low titer and disappear when the viral infections are cleared by the host immune system, and thus are probably not involved in the disease process. Cell-mediated immune reactions against autoantigens (CMAI) however persist longer, but their pathogenic role is largely unknown. Such CMAI has been well documented in disseminated postinfectious encephalomyelitis, in measles encephalitis, or

following rabies vaccination (Hemachudha et al., 1987). Both clinical disease and neuropathological changes may be mediated by autoantigen-specific immune reactions similar to what is observed following the adoptive transfer of MBP-specific T cells and subsequent induction of EAE in rats and mice. Indeed, measles virus infection of Lewis rats leads to both subacute and acute disease processes of the CNS. Animals developing such subacute measles encephalitis contain T cells primed for MBP, MBP-specific CD4+ cells, which when adoptively transferred to naïve syngeneic recipients cause EAE (Liebert et al., 1988). Similar findings have been reported in JHM coronavirus-induced subacute demyelinating encephalitis (Watanabe et al., 1983). The finding that viral infections may enhance the susceptibility to EAE has been made in another set of studies showing that a preceding infection with either measles virus or Semliki Forest virus potentiates both the development and severity of EAE. To explain these later findings, several hypotheses have been proposed. First, the virus-induced damage to CNS tissue facilitates the subsequent priming of clonal expansion of preexisting myelin-reactive T cells. Secondly, in measles virus infection, it is possible that cell-surface alterations occur in infected cells resulting in the exposure of cellular components together with the viral envelope proteins (Notkins et al., 1984). Such exposure of cellular antigens in infected brain cells could potentially lead to the development of immunity to fragments of MBP that do not normally elicit immunogenic responses. Thirdly, as a result of viral infection there are changes in the integrity of the BBB, which can allow the entry of antigen-specific CD4+ T cells into the CNS.

4.1 Molecular Mimicry as a Possible Cause of Autoimmunity within the CNS

The term "molecular mimicry" was originally formulated by Damian in 1964 to describe the phenomenon of shared antigens between host and parasite (Damian, 1987). If an infectious agent possesses an antigenic determinant that is similar to a host molecule, the determinant may not evoke an immune response or may be recognized as foreign and an immune response elicited that also attacks the host antigen. The degeneracy of the T-cell repertoire may account for the occurrence of molecular mimicry at the T-cell level. There are several instances of molecular mimicry in autoimmune diseases of the CNS. In herpes-induced keratoconjunctivitis, T cells with specificity for the viral protein UL6 cross-react with a corneal antigen (Zhao et al., 1998). In patients with Guillian–Barre syndrome following gastrointestinal infection, antibodies raised against *Campylobacter jejuni* cross-react with human gangliosides (Yuki, 1999). T cells, isolated from multiple sclerosis (MS) patients and shown to recognize MBP, also react with peptides derived from Epstein Barr virus, influenza type A, and human papillomavirus (Wucherpfennig and Stominger, 1995).

4.2 Autism as an Autoimmune Disease

Since autoimmune diseases are sometimes suspected of being triggered by viruses, recently investigators have been interested in virus serology in autism. Very little is known concerning the etiology or pathogenesis of this disorder that affects over half a million Americans alone. Current theories include genetic factors, immune factors, environmental factors, and neural factors. It has been found that many children with autism have elevated levels of antibodies to measles virus, but not to human herpes virus-6, cytomegalovirus, or rubella virus (Singh et al., 1998; Singh, 2001). The elevated levels of measles antibodies were associated with brain autoantibodies, which led the authors to postulate a pathogenic association of measles virus to autoimmunity in autism (Singh et al., 1998; Singh, 2001). Additionally these same authors found that several children with autism had unusual measles–mumps–rubella (MMR) antibodies, which showed a temporal association with MBP autoantibodies that were used as a marker of CNS autoimmunity in autism (Singh et al., 2001). Although the association between autism and autoantibodies is controversial, these findings are reported here since it is important to explore the possibilities of viral autoantibodies and human diseases. Indeed, it may be relevant in future research to characterize the molecular basis of cellular and humoral immunity to viral antigens in children with autism.

4.3 Lyme Disease

Lyme disease is caused by the spirochete *Borrelia burgdorferi*, and is primarily transmitted to humans by ticks. The disease is presented by a wide variety of symptoms including fever, a skin "bulls-eye" and has rheumatological as well as neurological consequences. The neurological problems are due to inflammation of the central and peripheral nervous systems. Oligoclonal bands (OCB) of immunoglobulin with restricted heterogeneity are often observed in cerebrospinal fluid (CSF) samples. Phage lambda gtll expression libraries from *B. burgdorferi* and human brains were screened with CSF antibody probes from patients with Lyme disease. It was found that patients produced antibodies against *B. burgdorferi* as well as CNS proteins. It is possible that this autoimmune response may be essential for the development of demyelinating disease in neurological Lyme borreliosis (Schluesener et al., 1989).

4.4 Acute Disseminated Encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is a demyelinating disorder of the CNS sharing many similarities with MS. Demyelination in MS is considered to be an autoimmune process mediated by autoreactive T cells against myelin epitopes. It has been postulated that in ADEM there is in vivo activation of autoreactive T cells by superantigens of *Streptococcus pyogenes* resulting in a dramatic demyelination. In vitro analysis of monocytes and T-cell clones indicated that: first, the T-cell receptor (TCR) repertoire was compatible with in vivo expansion induced by *S. pyogenes* exotoxins; secondly, MBP-reactive T cells showed cross-reactivity to *S. pyogenes* supernatant and exotoxins; thirdly, cytokine mRNA expression revealed a Th2-biased cytokine profile (Jorens et al., 2000). Thus, it was concluded that *S. pyogenes* may have induced activation of pathogenic myelin-reactive T cells contributing to the dramatic inflammatory demyelination.

4.5 Sydenham's Chorea

Some infectious agents directly invade the CNS, whereas others cause an immune-mediated disorder of the CNS without direct CNS invasion by the microorganism. The classic postinfectious disorder of the CNS is Sydenham's chorea (SC) (Sydenham, 1848), a psychiatric disorder occurring after infection with Group A streptococcus (GAS). In post-streptococcal CNS disease, several different immune mechanisms could cause dysfunction of the CNS including toxin-, T-cell-, B-cell-, antibody-, cytokine-, or superantigen-mediated disease. Elevated levels of antineuronal antibodies have been reported in 46% of patients with acute SC (Husby et al., 1976), and only 1.8% to 4% are controls. Further studies have supported antibody reactivity in acute SC (Morshed et al., 2001). However, the presence of autoantibodies in serum, and CSF, is only one inclusion criterion for an autoimmune-mediated disorder. Several studies support the presence of antineuronal antibodies and their pathogenicity in post-streptococcal disease in the CNS (Dale, 2005). The role of cellular immunity in SC has so far not been examined, but could be of critical importance. It is possible that several different immune mechanisms could result in the clinical symptoms of SC, complicated further by genetic, environmental, or neurochemical factors. However, despite these complications post-streptococcal disorders of the CNS remain an intriguing model of neuropsychiatric disease.

4.6 Protective Effects of Bacterial and Helminth Infections in CNS Disease

Interestingly, certain bacterial or helminth infections can result in a reduction in autoimmunity in the CNS. For example, it has been shown that during experimental infection with BCG (the vaccine strain of *Mycobacterium bovis*) overexpansion of activated CD4+ T cells is prevented by the interferon-γ (IFN-γ)-dependent promotion of apoptosis within this population (Dalton et al., 2000). Controlled elimination of Th1 cells is necessary to avoid the pathologies related to overaccumulation of these cells. The protective effect of BCG infection has been analyzed in an EAE model of human MS. In this model, the fate of genetically marked encephalitogenic CD4+ T cells was determined after transfer to BCG-infected and -uninfected recipients (O'Connor et al., 2005). The results support the hypothesis that the protection

conferred by mycobacterial infection results, in part, from the generation of an internal environment that is hostile to the survival of activated CD4+ T cells. Other bacteria showing a protective effect in reducing autoimmunity in the CNS include *Bordetella pertusis, Mycobacterium tuberculosis*, and *M. bovis* BCG. These findings have implications for autoimmune-, atopic-, vaccine-, and pathogen-induced immune responses during chronic mycobacterial infections.

In contrast to most bacterial infections, helminth infections induce a Th2-type immunity (Pearlman et al., 1993). The correlation between helminth infections and a lower incidence of autoimmune diseases has been suggested by several studies, most notably in MS. For example, MS occurs rarely in areas endemic with shistosome infections. Thus, it is possible that "natural Th2 preconditioning" could influence the development of Th1-modulated autoimmunity in the CNS. Indeed in experimental mice where a Th2 environment was induced, by intraperitoneal and subcutaneous *Schistosoma mansoni* ova immunization, there was a significant protection from EAE (Sewell et al., 2002). Since some intestinal helminthic infections produce little pathology, infection or treatment with helminth components has potential therapeutic applications for CNS autoimmunity, including MS. Other parasites that have been shown to have protective effects in autoimmune disease include *S. mansoni* live infection or ova, *Trypanosoma brucei brucei*, Malaria, and *Trichuris trichuria*.

5 Autoimmunity in Human Neurological Diseases

Several human neurological diseases, apart from MS, have been identified as probably involving autoimmune mechanisms. Such diseases include neuromyelitis optica (NMO), encephalitis lethargic syndrome, neuromyotonia (NMT), and possible schizophrenia. The most intensively studied disease in this group is "stiff-man syndrome" (SMS).

5.1 Neuromyelitis Optica

NMO, also known as Devic's disease, is an idiopathic demyelinating disease of the CNS, and is characterized by attacks of optic neuritis and myelitis. Although the causes of NMO are unknown, several lines of evidence suggest the involvement of B-cell autoimmunity. In human cases, the lesions are seen in the spinal cord and optic nerves. Analysis of these lesions indicated that demyelination was present across multiple spinal cord levels, associated with cavitation, necrosis, and acute axonal pathology (spheroids) in both gray and white matter (Lucchinetti et al., 2002). The inflammatory infiltrates in the lesions are characterized by macrophages associated with large numbers of perivascular granulocytes and eosinophils, together with rare CD3(+) and CD8(+) T cells. Active lesions show a marked perivascular deposition of immunoglobulins and complement C9 neoantigen. Additionally, there is serum autoantibody NMO-IgG in active patients (Wingerchuk, 2006). These findings taken together support a role for humoral immunity in the pathogenesis of NMO.

5.2 Neuromyotonia

There is increasing evidence that autoimmunity is implicated in the pathogenesis of peripheral nerve hyperexcitability, neuromyotonia (NMT). In NMT, patient's plasma or IgG can transfer the electrophysiological features to mice, and can reduce voltage-gated potassium channel currents in vitro. Indeed antibodies to voltage-gated potassium channels can be detected in the serum of many patients, who have peripheral nerve hyperexcitability. Thus, NMT can occur as antibody-mediated autoimmune ion channelopathies like myasthenia gravis and the Lambert–Eaton myasthenic syndrome (Newsom-Davis, 2004). These findings offer alternative approaches to the treatment of NMT.

5.3 Schizophrenia

Research on schizophrenia has focused on studies of structural and functional brain abnormalities, but recently has changed direction with the emphasis on possible etiological factors. One hypothesis is that schizophrenia is caused by an infection or is the result of an autoimmune reaction against the CNS. Several

studies attempted to identify a specific infection agent or an antibody directed against CNS tissue have not produced a consistently replicable finding (Kirch, 1993). However, schizophrenia is more likely to be a heterogeneous disorder resulting from multiple factors including genetic, environmental factors, as well as autoimmune mechanisms.

5.4 Lethargic Encephalitis

Lethargic encephalitis has been known for centuries and the most recent epidemic ravaged the world between 1916 and 1927, and was named by von Economo as encephalitis lethargica (EL) (Von Economo, 1931). Since EL was epidemic during the same period as the 1918 influenza pandemic, it was originally proposed that EL was caused by influenza virus. However, recent reports have consistently failed to demonstrate evidence of neurotropic viral particles. The finding of OCB in the CSF (Williams et al., 1979), and the successful treatment of some cases with steroids, has led to the hypothesis that this phenotype may be immune-mediated. Recently, cases of an EL-like syndrome have been reported, often following pharyngeal infections. These EL-like patients have been examined for the presence of autoantibodies, particularly against basal ganglia (Dale et al., 2004). It was found that either intrathecal OCB or a mirrored pattern of OCB was seen in 69% of the patients. By contrast, all CSF PCR studies were negative suggesting that a neurotropic viral encephalitis is unlikely. Histopathological findings in EL show perivenous lymphocytic cuffing of the basal ganglia. Cellular infiltration consists of both T and mature B lymphocytes. Additionally, there were secondary reactive astrocytes and macrophage activation but no other striking pathological features. The hypothesis that the EL phenotype could be etiologically similar to Syndenham's chorea is appealing. In EL, it is possible to demonstrate autoantibodies reactive against discrete basal ganglia autoantigens in 95% of the patients (Dale et al., 2004). CSF examination confirmed that the autoantibodies are present in the CNS, although at present it is unknown whether these antibodies are produced either intrathecally or peripherally. Future proteomic studies should be able to identify the auto antigens involved. Dale has proposed that this EL phenotype may occur secondary to postinfectious autoimmunity with vulnerability of deep gray matter neurons (Dale et al., 2004).

5.5 Stiff-Man Syndrome

SMS is a rare human CNS disease, characterized by chronic rigidity of the body musculature with superimposed painful spasms (Moersch and Woltman, 1956). Although the etiology of SMS is unknown, an autoimmune mechanism has been postulated based on the presence of autoantibodies against γ-aminobutyric acid (GABA)-converting enzyme glutamic acid decarboxylase (GAD) in up to 60% of SMS patients (Solimena et al., 1990). The pathogenic significance of these autoantibodies is uncertain. The frequent finding of pancreatic autoreactivity in SMS patients and the higher than predicted association of SMS with INS-dependent diabetes mellitus (IDDM) suggests that these two diseases might have an autoimmune pathogenesis involving shared autoantigens predominantly expressed in neuron–endocrine tissues such as the brain and pancreas (Solimena and De Camilli, 1991). To further refine the role of autoimmunity in SMS, the autoimmune recognition of a second IDDM-associate autoantigen, pancreatic 37/40-kDa IDDM autoantigen (coded for by the gene called ICA), has been investigated (Martino et al., 1996). Human ICA 105 is restricted to the pancreas and brain and its distribution within the CNS is similar to GAD. Anti-ICA 105 and anti-GAD antibodies have been detected in 75% of patients with SMS. Thus ICA 105 represents another putative neuroendocrine autoantigen in SMS.

In a subset of cases, SMS has an autoimmune paraneoplastic origin. The presence of high-titer autoantibodies directed against gephyrin has been reported in a patient with clinical features of SMS and mediastinal cancer (Butler et al., 2000). Gephyrin is a cytosolic protein selectively concentrated at the postsynaptic membrane of inhibiting synapses, where it is associated with GABA and glycine receptors. It has been suggested that these mixed GABA/glycine synapses are the primary targets of autoimmunity in SMS. The question remains as to how these autoantibodies arise? It is possible that T cells or other

associated antibodies directed against surface antigens may mediate the disease. These autoantibodies could be generated by the spread of an autoimmune response against macromolecular complexes, including both surface antigens and associated intracellular proteins.

6   Autoimmunity Caused by CNS Insult

Injury to nerves, such as transection or crush injury, can result in autoimmune reactions. Examples of such injury are best shown in studies with rats involving facial nerve transaction and optic nerve crush injury.

Nervous tissue expression of immunological signaling molecules and lymphoid tissue immune responses has been studied in male rats of the Lewis and Brown Norway (BN) strains following facial nerve transection (Olsson et al., 1992). Within 4 days of nerve transection, in both strains of rat, IFN-γ-like immunoreactivity was detected in the cytoplasm of axotomized motor neurons. In addition, there was a similar induction of MHC class I and class II and CD4 molecules on surrounding glial cells. T-lymphocyte infiltration was also observed in the facial nuclei ipsilateral to the axotomoy in all rats. Autoreactive T cells, to myelin or peptides of MBP, secreting IFN-γ, increased markedly in the superficial cervical lymph nodes. Some, but not all, of the axotomized Lewis rats developed widespread perivascular infiltration of mononuclear cells in the CNS. This later finding, reminiscent of EAE, may have immunological consequences.

Spinal cord injury (SCI) initiates many destructive processes mediating tissue injury at the site, and in close proximity, of primary trauma. These processes are collectively referred to as secondary injury. Several lines of evidence implicate immunologic activation in promoting progressive tissue pathology and/or inhibiting neural regeneration after traumatic injury to the CNS. The significance of immune cells within the spinal cord lesions remains somewhat controversial. Lymphocytic infiltration is also observed after CNS injury. Since myelin-reactive antibodies are elevated following CNS injury, both B and T cells are likely to be activated (Palladini et al., 1987). These findings, coupled with pathophysiologic data, show a striking resemblance between SCI and inflammatory demyelinating diseases such as EAE (Popovich et al., 1996). Witebsky postulated that three criteria need to be fulfilled to establish the autoimmune nature of a disease (Rose and Bona, 1993). First, disease induction in normal individuals must be effected by the transfer of autoreactive antibodies or autoreactive T cells. Secondly, evidence must be obtained by reproducing the disease in animals. Thirdly, autoantibodies and/or autoreactive T lymphocytes must be isolated from the diseased organ. In SCI, data show that the second criteria is satisfied and experimental results fulfill the third condition, namely, CNS-reactive antibodies have been isolated from both animals and patients with SCI (Palladini et al., 1987). Additionally, low-level T-cell proliferation to MBP has been measured after SCI, as well as the generation of encephalitogenic T cells (Popovich et al., 1996). However, in SCI immunopathogenic responses are rare. Autoimmune reactions occurring after SCI could be due to T-cell recognition of myelin, which contains proteins that are normally sequestered behind the BBB in adults. It is highly likely, as in other autoimmune diseases, that both genetic and environmental factors play a role in the outcome of SCI.

7   Autoimmunity as a Mediator of CNS Repair

Rather than being purely deleterious, it is possible to use autoimmunity as a tool to mediate CNS repair.

7.1 Antibody-Mediated Remyelination

It has clearly been demonstrated that autoreactive antibodies can enhance endogenous myelin repair in the Theiler's virus model of MS (Bieber et al., 2001). Intracerebral inoculation of Theiler's murine encephalomyelitis virus (TMEV) into susceptible SJL mice results in acute encephalitis that is resolved in 14–21 days, which is followed by chronic viral persistence. This persistent TMEV infection leads to chronic demyelination and loss of motor function, and is used as an animal model of human MS. In the SJL strain, demyelination is

evident within 30 days after infection, and paralysis eventually occurs by 6–9 months. Spontaneous remyelination is very limited in SJL mice, where <10% of the total demyelinated lesion is repaired. Thus, SJL mice make an excellent model to study strategies promoting remyelination. In this model, it was found that transfer of antiserum or purified immunoglobulin (Rodriguez and Lennon, 1990) from uninfected animals immunized with spinal cord homogenate (SCH) enhanced remyelination, demonstrating a beneficial role for the humoral immune response against SCH in promoting myelin repair. Hybridomas were subsequently generated from SJL mice following SCH immunization. Two mouse monoclonal antibodies (mAbs) were identified that enhance this remyelination and are polyreactive IgM antibodies. These mAbs bind to antigens expressed on the surface of oligodendrocytes, suggesting that the remyelinating promoting activity of these mAbs involve the direct stimulation of myelin-producing cells (Asakura and Rodriguez, 1998).

7.2 MBP-Specific T Cells Aid Recovery from Spinal Cord Damage

Since the CNS is termed an "immune-privileged site," immune responses with the CNS are restricted (Streilein, 1995). In the CNS, under normal conditions, activated T cells can cross the BBB and enter the CNS parenchyma. However, only T cells capable of reacting with a CNS antigen persist there (Hickey et al., 1991). Following axotomy in the CNS, there is a significantly greater accumulation of endogenous T cells in the injured PNS axons than in the injured CNS axons. In addition, the CNS shows a high potential for elimination of T cells via apoptosis (Smith et al., 1996), whereas such elimination is less effective in the PNS and other tissues. These findings taken together have led investigators to conclude that the T-cell response to CNS injury is limited, and has raised the question of whether boosting the T-cell response at the site of CNS injury can affect the outcome of secondary degeneration. Studies with Lewis rats, subjected to spinal cord contusion at T7 or T9 and given systemic injection of anti-MBP T cells at the time of contusion, or 1 week later, results in significantly better recovery than that observed in control rats treated with T cells directed against ovalbumin (Hauben et al., 2000). Not only passive T-cell transfer but also active immunization with MBP promotes recovery from SCI. The earlier results raise various questions concerning the mechanism of this neuroprotective effect. Results with thymectomized rats and nude mice demonstrate that the observed neuroprotection is T-cell-dependent (Yoles et al., 2001), although the precise type of T cell involved is as yet unclear. The beneficial T cells might operate by producing cytokines and neurotrophic factors, whose primary targets are probably astrocytes, microglia, and even neurons. Regardless of the mechanism of the T-cell-mediated neuroprotective effect, the experimental evidence clearly shows that active or passive immunization with CNS myelin-associated antigens can be beneficial for neuronal recovery (Schwartz and Cohen, 2000). The nature of the regulatory mechanism controlling beneficial autoimmunity has yet to be elucidated. A number of endogenous mechanisms have been proposed (Schwartz, 2001), and the role of such mechanisms in neuronal protection should be examined.

8   Multiple Sclerosis

MS is the most common demyelinating disease of the CNS occurring at a prevalence of 250,000–350,000 in the USA (Anderson et al., 1992) and the national annual costs of this disease were estimated to be $6.8 billion (Whetten-Goldstein et al., 1998). MS usually affects people between the ages of 15 and 50, although there is an increasing number of juvenile MS patients who develop disease. Eighty percent of MS patients have a relapsing–remitting disease, which eventually progresses to a chronic progressive disorder. The MS lesion is characterized by plaques throughout the white matter of the brain and spinal cord. Demyelination is accompanied by inflammatory cell infiltrates consisting of plasma cells, macrophages/microglia, T and B lymphocytes. In common with other autoimmune diseases, relapsing–remitting MS is more common in women than men, with a ratio of 2:1. Autoimmune responses to myelin components MBP, PLP, and MOG have been detected in MS patients, suggesting an autoimmune etiology for MS (Stinissen et al., 1997).

MS is a complex disease which follows a markedly varying course in different patients and also patients' responses to therapy vary considerably. Recently, MS lesions have been classified into four separate

categories, which may account for the heterogeneity in disease (Lucchinetti et al., 2000). Type I MS lesions were similar to T‐cell‐mediated demyelination and type II lesions resembled T‐cell plus antibody‐mediated autoimmune encephalomyelitis. Type III and IV lesions involved primary oligodendrocytes dystrophy (virus‐ or toxin‐induced).

9 Experimental Autoimmune Encephalomyelitis

EAE is the most widely used animal model of MS. EAE was first developed in 1933 (Rivers et al., 1933). Originally, the disease was induced by injections of whole brain or spinal cord homogenates with adjuvants (Kabat et al., 1947). However, more recently encephalitogenic CNS proteins or peptides have been used to induce EAE. This disease is mediated by CD4+ T cells that recognize certain myelin epitopes and infiltrate the CNS causing inflammatory demyelination.

In order for a T‐cell clone to be pathogenic and induce EAE, it must home to the target organ, recognize antigen within target tissue, and produce a combination of cytokines to initiate tissue injury. The first critical step in this process is the interaction of lymphocytes with the cerebrovascular endothelial cells (CVE). The interaction between CVE and T lymphocytes is mediated by a number of different adhesion molecules: lymphocyte functional antigen‐1 (LFA‐1) binding to intracellular adhesion molecule‐1 (ICAM‐1) and ICAM‐2, VLA‐4 to VCAM‐1 and fibronectin. Experiments with encephalitogenic T‐cell clones to MBP (Kuchroo et al., 1993) and PLP (Barten and Ruddle, 1994) have shown increased expression of adhesion molecules (in particular VLA‐4) and tumor necrosis factor (TNF) contribute to the pathogenicity of the T cells.

10 A Viral Etiology for Multiple Sclerosis

The etiology of MS is unknown, although epidemiological studies have implicated an infective agent as a probable initiating factor (Acheson, 1977; Gilden, 2001). An epidemiological survey reported that the increased risk of developing MS was associated with mumps, measles, and Epstein‐Barr virus infections at an older age (Miguel et al., 2001). In addition, exacerbations of MS are frequently preceded by viral infections (Sibley et al., 1985). It is also intriguing that the antiviral agent IFN‐β has been reported to have a beneficial effect on relapsing–remitting MS (IFN‐β Multiple Sclerosis Study Group, 1993). IFN‐β also inhibits the progression of relapsing–remitting EAE in mice (Yu et al., 1996). The exact mechanism of IFN action in these conditions is not completely understood. IFN‐β has many diverse biological roles ranging from antiviral to immunomodulatory effects (Belardelli and Gresser, 1996). Since MS is thought to be initiated by a viral infection, the effectiveness of IFN may be related to its role in viral inhibition. However, the autoimmune aspects of MS may be downregulated through a number of different mechanisms because type I IFNs have been shown to inhibit DTH responses (also important in Theiler's virus‐induced demyelination (TVID) and EAE); alter the homing and trapping of lymphocytes; enhance NK and T‐cell activity and cytotoxicity; enhance Fcγ receptors effects (Belardelli and Gresser, 1996); inhibit T‐cell proliferation; and decrease the production of IFN‐γ (Noronha et al., 1993). IFN‐β has also been shown to decrease the migration of T lymphocytes in vitro by interfering with the production of T‐cell matrix metalloproteinases, which mediate T‐cell migration through matrices. Both NK cells, CD8 and CD4 T cells, were also affected by this treatment. The authors demonstrated that IFN‐β decreased the matrix metalloproteinase levels which in turn prevented the cleavage of fibronectin (Stuve et al., 1996).

A number of different viral agents have been isolated from the brains of MS patients, including measles, mumps, parainfluenza type I (Allen and Brankin, 1993), and human herpes simplex type 6 (HHSV6) (Challoner et al., 1995). In common with other autoimmune diseases, stressful life events may precipitate the onset and clinical relapses in MS patients (Whitacre et al., 1994). One mechanism of stress‐induced exacerbation might be via increased glucocorticoid levels resulting in immunosuppression and reactivation of latent viruses such as herpes virus.

Viruses are also known to cause demyelination in animals: measles virus in rats; JHM mouse hepatitis virus, Semliki Forest virus, and Theiler's virus in mice; visna in sheep; herpes simplex in rabbits

(Dal Canto and Rabinowitz, 1982). Therefore, in order to understand the pathogenesis of MS, animal models of virus-induced demyelination such as Theiler's virus infection represent a highly relevant approach. Theiler's virus infection in mice is not only an excellent model for the study of the pathogenesis of MS, but also a model system for studying disease susceptibility factors, mechanisms of viral persistence within the CNS, and virus-induced autoimmune disease.

11   Theiler's Murine Encephalomyelitis Virus as a Model for MS

Max Theiler first described TMEV in 1934 after isolating this virus from the brain of a paralyzed mouse (Theiler, 1934). Theiler noted that the incubation period was 7–30 days and the mice remained infected up to 150 days after injection. The mice developed acute necrosis of the ganglion cells in the anterior horn of the spinal cord. TMEV was originally classified as an enterovirus in the Picornaviridae family, as it was biologically similar to poliovirus. However, after the sequencing of TMEV, it was reclassified as a cardiovirus as it showed marked similarity to mengovirus.

11.1 Age-Related Susceptibility to TVID

Theiler's virus infection in mice became a model for MS in the 1970s, after Lipton demonstrated that the virus induced inflammatory demyelination (Lipton, 1975). The virus is administered intracranially to mice that are 4–6 weeks of age because younger animals develop fatal encephalitis and older animals become resistant (Steiner et al., 1984). This window of opportunity is a common theme in neurotropic viral infections that induce demyelination. It is also interesting to note that exposure to the putative causative agent of MS occurs before or during adolescence. The susceptibility age phenomenon is probably not due to immune system development because mice and humans have mature immune systems during adolescence. A potential explanation is that there are a crucial number of oligodendrocytes at a susceptible time of development available for infection. Evidence to support this hypothesis is that mice are still actively myelinating at this stage and humans continue myelination until about 20 years of age. In addition, mature oligodendrocytes appear to be relatively resistant to TMEV infection in vitro whereas immature oligodendrocytes are susceptible to the lytic effects of TMEV (O'Shea et al., 1997).

11.2 The Early Disease Induced by Theiler's Virus

During early Theiler's virus infection, neurons are infected and, in resistant strains of mice, this early gray matter disease is the only manifestation of infection. However, in susceptible mice the virus also infects and persists in oligodendrocytes, astrocytes, and macrophages/microglial cells (Aubert et al., 1987; Blakemore et al., 1988). Theiler's virus must establish a persistent infection in the CNS to cause later demyelinating disease (Aubert et al., 1987). Strains of mice that are resistant to develop TVID are able to clear the early viral infection effectively from the CNS. Susceptible strains of mice fail to clear the CNS infection, in part due to inadequate natural killer cell (NK), cytotoxic T-cell (CTL) and CD4+ T cell responses (Borrow et al., 1992, 1993). During the early infection, virus replicates to high levels in the brain and spinal cord (Welsh et al., 1989). At ∼4 weeks postinfection, the viral titers decrease and this coincides with the development of high-neutralizing antibody titers. In this early phase of the disease, the virus infects neurons and mice may develop polio-like disease, that is, flaccid hind limb paralysis.

11.3 The Late Demyelinating Phase of Theiler's Virus Infection

The mechanisms of demyelination in the TVID model are complex. Demyelination is partly mediated by direct viral lysis of oligodendrocytes (Roos and Wollmann, 1984). CTL reactivity has also been implicated in demyelination (Rodriguez and Sriram, 1988). Bystander demyelination mediated by virus-specific DTH

T cells recruiting macrophages to the CNS is a further mechanism (Clatch et al., 1987; Gerety et al., 1991). Finally, autoimmunity, at both the B- and T-cell level, has been detected in TVID (Welsh et al., 1987, 1989, 1990; Miller et al., 1997; Borrow et al., 1998). The autoimmune reactivity seen in TVID may result from viral damage to oligodendrocytes, uptake and processing of myelin antigens by macrophage/microglial cells, and subsequent activation of autoreactive T cells. The autoreactive T cells have been shown to be pathogenic and are able to demyelinate in vitro (Dal Canto et al., 2000). Epitope spreading has also been noted in TVID whereby SJL mice first develop T-cell responses to viral epitopes, followed by T cells to PLP139–151 (the dominant encephalitogenic peptide in this strain of mice). Intramolecular epitope spreading to PLP178–191 and followed by PLP56–70 is then observed and finally intermolecular spreading to MOG92–106 (Miller et al., 1997).

11.4 Genetic Control of Susceptibility to TVID

A number of studies have reported that viral persistence and demyelination in susceptible strains of mice are under multigenic control. Overall there is good correlation between viral load, pathology, and clinical symptoms within different strains of mice infected with TMEV which suggests that the host's ability to control the viral replication during the persistent infection is related to disease status (Brahic et al., 2005). The most important genes implicated in susceptibility to demyelination are the MHC class I and the T-cell receptor genes (Melvold et al., 1987). Another gene locus on chromosome 6 not linked to the T-cell receptor locus has also been implicated in demyelination (Bureau et al., 1992). Two additional loci, one close to IFN-γ on chromosome 10 and one near MBP on chromosome 18, have been associated with viral persistence in some strains of mice (Bureau et al., 1993). Immune recognition of Theiler's virus is clearly an important element in susceptibility to demyelination, as indicated by the genetic association with MHC and the T-cell receptor, although other undefined factors are also involved.

11.5 Similarities between TVID and EAE

The lesions induced by Theiler's virus not only resemble those seen in EAE, but also occur in the same locations within the spinal cord (Blakemore et al., 1988). Similar strains of mice are susceptible to EAE and Theiler's virus; SJL mice being the most susceptible to both diseases (Linthicum and Frelinger, 1982; Rodriguez et al., 1986). Treatments of both diseases with immunosuppressive regimens and monoclonal antibodies to MHC class II (Steinman et al., 1981; Freidmann et al., 1987) and CD4 (Waldor et al., 1984; Welsh et al., 1987) have proved successful. Interestingly, local x-irradiation of the spinal cord in EAE and Theiler's virus infection resulted in the exacerbation of the lesions probably through the increased permeability of the BBB (Love et al., 1987). Taken together, these facts indicate that there may be similar mechanisms of demyelination operating in both conditions. Furthermore, autoimmune phenomena occur in Theiler's virus-infected mice and autoreactive T cells have been shown to mediate demyelination in vivo (Dal Canto et al., 2000). Just as EAE has been transferred by the intravenous injection of T-cell clones against an encephalitogenic determinant (Ben-Nun et al., 1981), autoreactive T cells in TVID may also be an important part of the disease pathogenesis.

11.6 Aberrant MHC Class II Expression

The ability of antigen-presenting cells to express MHC class II antigens has been shown to be an important initiating event in the evolution of an immune response (Schwartz et al., 1978).

Aberrant class II expression occurs on both target cells and endothelial cells in a number of autoimmune diseases and is thought to be important either in the initiation of the inflammatory process or in the subsequent perpetuation of the disease process (Bottazzo et al., 1983).

The induction of class II expression on astrocytes has been found to correlate with susceptibility to demyelination induced by JHM virus and in EAE in SJL mice (Massa et al., 1987). The relevance of aberrant class II expression on astrocytes is unclear because the predominant antigen-presenting system in CNS is the microglia (Matsumoto et al., 1988). Furthermore, the class II-expressing astrocytes are able to present both MBP (Fontana et al., 1984) and viral antigens to T cells (Borrow and Nash, 1992). Astrocytes also express the ICAM-1 in response to a number of lymphokines (Frohen et al., 1989). This intergrin molecule is the ligand for LFA-1 and their association is intimately involved in antigen presentation.

The effectiveness of monoclonal antibodies directed at MHC class II antigens in the treatment of both EAE (Steinman et al., 1981) and TVID (Friedmann et al., 1987) also provides evidence of the importance of aberrant MHC class II expression and subsequent antigen presentation in the evolution of the inflammatory process. Presumably, the monoclonal antibodies are acting either at the BBB preventing MHC class II expression on the endothelial cells or in the lymphoid tissue interfering with T-cell activation.

Differential virus-induced MHC expression on cells within the CNS may also account for defective viral clearance from the white matter in TVID-susceptible mice and may explain why virus is confined to the gray matter in resistant strains of mice. MHC expression in the CNS is induced during TVID (Lindsley et al., 1992). MHC class I expression has been shown to be mediated by type I IFN, since IFN-α/β knock out mice fail to express MHC class I following infection with TMEV (Njenga et al., 1997). TMEV infection of SJL/J and CBA CVE results in the upregulation of expression of MHC class I on CVE (Sapatino et al., 1995; Welsh et al., 1995) via IFN-β production (unpublished data). In addition, IFN-γ upregulates the expression of MHC class II on CVE (Welsh et al., 1993) and astrocytes (Borrow and Nash, 1992) derived from strains of mice that are susceptible to TVID. Other researchers have demonstrated that the IFN-γ-inducible MHC class II expression in SJL CVE is confined to endothelial cells derived from the CNS (Jemison et al., 1993). Increased MHC class II expression on cells within the CNS may lead to increased antigen presentation and inflammation. The fact that there is a correlation between susceptibility to TVID and increased MHC expression in the CNS suggests that the CNS of autoimmune susceptible mice is a more inflammatory environment than that of TVID-resistant mice.

12 The Role of the BBB in TVID and MS

The BBB is composed of CVE, astroglia, pericytes, perivascular macrophages, and basal lamina. In inflammatory conditions of the CNS such as MS, and two animal models of MS: EAE and TVID, T cells enter the CNS and mediate tissue damage. Lymphocyte cuffing around postcapillary venules is a characteristic of all these conditions and suggests that the main route of cellular migration (and viral migration in the case of TVID) may occur across the BBB. Heterotropic brain transplants from EAE-susceptible (SJL/J) to resistant mouse strains suggest that regulation of susceptibility to disease resides at the level of the cerebral endothelium and not within the CNS parenchyma or lymphoid/bone marrow-derived compartment (Goldowitz et al., 1987). Therefore, the BBB is critical in the development of inflammatory CNS disease.

The role of CVE in MS is likely to be more important than originally suspected. In progressive MS, there is rapid trafficking of T cells from the vasculature across the BBB and into the CNS (Hafler and Weiner, 1987). Furthermore, antibodies to CVE were described in MS patients (Tanka et al., 1987) and rhesus monkeys injected with CVE were shown to develop EAE (Tsukada et al., 1988). In patients with MS, therapy with IFN-γ caused exacerbations which may have resulted from increased MHC class II expression on CVE (Panitch et al., 1987) and subsequently, antigen presentation which would allow increased access of T cells into the CNS. Interestingly, cytotoxic activity against CVE has also been described in MS patients (Tsukada et al., 1993).

12.1 Demyelinating Viruses and the BBB

A number of viruses that have been implicated in MS have been shown to infect CVE. CVE possess many specialized receptors (transferrin receptor, γ-GTP, acetylated LDL) that may also function as specific viral receptors. Infection of CVE may allow the virus to gain access to the CNS or may result in the upregulation

of various molecules involved in lymphocyte adhesion. Herpes simplex virus infection of CVE causes an upregulation in the expression of ICAM-1 and increased adhesion of naive syngenic splenocytes (Brankin et al., 1995). Alteration in the function of the BBB may also result from systemic infection with virus resulting in increased cytokine production. It is interesting to note that MS patients often suffer from disease relapses following viral infections (Sibley et al., 1985).

Interactions at the BBB in Theiler's virus infection have been shown to be important in the development of demyelinating disease. Hyperexpression of ICAM-1 on vascular endothelial cells was observed in the spinal cord of TMEV-infected mice and suppression of TVID was observed following treatment with monoclonal antibody to ICAM-1 or LFA-1 (Inoue et al., 1997a). In addition, fibrin deposition within the spinal cord correlated with the degree of demyelinating disease seen in SJL mice infected with TMEV, indicating that increased permeability of the BBB is an important component in TVID neuropathogenesis (Inoue et al., 1997b).

13 Mast Cells in Demyelination

Susceptibility to both TVID and EAE is controlled by a number of genes including those for MHC and T-cell receptors. In addition, genes for vasoactive amine (VAA) sensitization have been implicated in susceptibility to EAE (Linthicum and Frelinger, 1982) and the administration of cyproheptadine (a serotonin and histamine blocker) has been shown to reduce the edema and inflammation in this condition (Waxman, et al., 1984). The strains of mice that are susceptible to EAE and TVID are also sensitive to VAA and therefore VAA may also play a role in the development of TVID. One possible source of VAAs in the CNS is mast cells which have been demonstrated in the thalamus, hypothalamus, meninges, and in close proximity to the dorsal root ganglia in association with blood vessels (Orr, 1988). It is precisely at these sites that demyelination occurs in both EAE and TVID (Blakemore et al., 1988). Regional and temporal increases in the histamine content of the brain and spinal cord occur concomitantly with the appearance of EAE in the rat (Orr and Pace, 1984). Furthermore, mast cells have been shown to be essential for the early onset and severity of disease in EAE using mast cell-deficient mice (Secor et al., 2000). Mast cells are regularly present in the border zone of MS plaques in close association with small vessels but are absent from normal brain tissue (Kruger et al., 1990). Recently, BBB abnormalities were detected not only in focal lesions but also in diffusely abnormal white matter as detected by postmortem MRI (Vos et al., 2005). Interestingly, hydroxysine, a histamine-1 (H1) receptor antagonist, has been shown to be effective in EAE and a recent pilot clinical trail in MS has shown promising results (Logothetis et al., 2005).

The role of VAAs in CNS inflammation is hypothesized to be related to their ability to increase the permeability of the BBB allowing the influx of elevated numbers of T cells into the CNS. TNF-α-secreting CD4+ T cells specific for MBP have been shown to cause EAE (Ben-Nun and Cohen, 1971; Powell et al., 1990) and similar Th1 virus-specific T cells have been implicated in the pathogenesis of TVID (Clatch et al., 1987). Thus, the passage of these cells into the CNS is an important initiating event in the pathogenesis of both conditions. Mast cells secrete and release TNF-α that has been shown to cause myelin loss by direct toxic effect on oligodendrocytes (Selmaj and Raine, 1987). In addition, activated mast cells have been shown to secrete proteases that also destroy myelin (Theoharides, 1990). Furthermore, the mast cell proteases release an encephalitogenic peptide from MBP (Johnson et al., 1998) that can be presented to T cells by either astrocytes or endothelial cells and cause T-cell proliferation.

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