Animal Models of Autoimmune Neuropathy

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Abstract

The peripheral nervous system (PNS) comprises the cranial nerves, the spinal nerves with their roots and rami, dorsal root ganglia neurons, the peripheral nerves, and peripheral components of the autonomic nervous system. Cell-mediated or antibody-mediated immune attack on the PNS results in distinct clinical syndromes, which are classified based on the tempo of illness, PNS component(s) involved, and the culprit antigen(s) identified. Insights into the pathogenesis of autoimmune neuropathy have been provided by ex vivo immunologic studies, biopsy materials, electrophysiologic studies, and experimental models. This review article summarizes earlier seminal observations and highlights the recent progress in our understanding of immunopathogenesis of autoimmune neuropathies based on data from animal models.

Key Words: anti-ganglioside antibodies; chronic inflammatory demyelinating polyradiculoneuropathy [CIDP]; experimental autoimmune neuritis [EAN]; Guillain-Barré syndrome; inflammatory neuropathy; myelin proteins; spontaneous autoimmune polyneuropathy [SAP]

Introduction

Immune-mediated attacks on the peripheral nervous system (PNS) can manifest as Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), antibody (Ab)–mediated neuropathies, sensory neuronopathy, autonomic neuropathy, or vasculitic neuropathy. Although the triggering mechanisms are not completely understood, existing evidence supports the concept of molecular mimicry in some forms of autoimmune neuropathy, particularly those that are often preceded by an infection. Surface lipo-oligosaccaharide structures of *Campylobacter* and other microbial species mimic PNS gangliosides, which have been identified as the antigenic target in some GBS variants and chronic dysimmune neuropathies (Rinaldi and Willison 2008; Yuki et al. 2004). The most frequent form of GBS in Western countries is the so-called acute inflammatory demyelinating polyneuropathy (AIDP) that is characterized clinically by acute/subacute ascending paralysis, hyporeflexia with variable sensory involvement, and histopathologically by mononuclear infiltrates and segmental demyelination. Common GBS variants include Miller Fisher syndrome, acute motor axonal neuropathy (AMAN), and acute motor and sensory axonal neuropathy (Ho et al. 1998). CIDP can be relapsing–remitting or progressive, with the nadir of maximal neurologic deficit reached after 8 weeks or longer from the onset. Our understanding of GBS and CIDP has been greatly enhanced by pathologic studies on biopsy and autopsy materials and immunologic studies on human samples over the last two decades (Ho et al. 1998; Koller et al. 2005). In subsequent sections, we will focus on immune mechanisms that trigger the development of inflammatory neuropathies in animals.

Induced Models of Autoimmune Neuropathy

Experimental Autoimmune Neuritis

Experimental autoimmune neuritis (EAN), a widely accepted model of GBS and CIDP, can be induced in animals by immunization with peripheral nerve homogenate or by immunization with PNS myelin proteins (e.g., P0, P2, and PMP22). After a latent period of about 2 weeks, animals develop ataxia and weakness (Brostoff et al. 1977; Gabriel et al. 1998; Milner et al. 1987; Rostami et al. 1990; Waksman and Adams 1955; Zou et al. 2000). EAN can be induced in rats, mice, rabbits, and guinea pigs and is typically monophasic with a few exceptions. A biphasic form of EAN in dark Agouti rats can be induced with bovine peripheral nerve myelin in complete Freund's adjuvant (Jung et al. 2004).

EAN as an experimental model has been criticized for its failure to translate to successful identification of the antigenic target(s) of autoreactive T cells in GBS and CIDP. In spite of the above shortcomings, EAN has provided valuable information regarding immune mechanisms contributing to inflammatory neuropathies, such as identification of neuritogenic epitopes, mechanisms involved in antigen recognition, the role of costimulatory signals, adhesion molecules and various cytokines, as well as mechanisms of injury

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(Koller et al. 2005; Maurer et al. 2002). For example, we have learned that EAN is alleviated in CD28-deficient C57BL/6 mice immunized with P0 peptide 180-199 (Zhu et al. 2001). Recovery from EAN coincides with increased interleukin 10 (IL-10) expression and is associated with T cell apoptosis (Jander et al. 1996; Zetti et al. 1996; Zhu et al. 1997).

The pathology of EAN closely resembles that of AIDP and CIDP. In the rat, perivascular T cell infiltrates appear around 10 to 12 days after immunization and 2 to 3 days before myelin destruction and onset of paralysis (Astrom et al. 1968). The successful transfer of disease with lymph node cells from immunized animals or with P2-specific T cell lines led to the assumption that GBS and CIDP are primarily T cell–mediated diseases (Hughes et al. 1981; Linington et al. 1984). This popular view has been challenged to some extent by the discovery of antiglycolipid Abs in GBS variants and chronic dysimmune neuropathies.

The second prominent invading cell type in EAN, GBS, and CIDP is the monocyte, which becomes activated to a macrophage by cytokines secreted by T cells. Macrophages are the main effector cells that strip myelin or cause nerve injury by reactive oxygen species, proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), nitric oxide, or production of complement. Protection against EAN can be induced by depletion of macrophages by intraperitoneal injection of silica dust or by blocking macrophage function with cyclooxygenase inhibitors (Hartung et al. 1988; Tansey and Brosnan 1982). EAN is attenuated in TNF-α knockout (KO) mice, which is associated with an altered balance of M1/M2 macrophages (Zhang et al. 2012).

Aside from T cells and macrophages, there is evidence that B cells contribute to the pathogenesis of EAN by CD40L–CD40 interactions and regulatory mechanisms. B cells play a suppressive role during the induction of EAN but enhance the severity of EAN during peak disease (Brunn et al. 2010; Zhu et al. 2007). Furthermore, there is evidence that Abs against peripheral nerve components contribute significantly to demyelination or conduction failure after the blood nerve barrier is disrupted by myelin protein/peptide-reactive T cells (Taylor and Pollard 2001).

Electrophysiologic findings in EAN include demyelinating features such as nerve conduction slowing, prolonged latencies, and conduction block, as well as varying degree of axonal involvement (Heininger et al. 1986; Rostami et al. 1984; Taylor and Pollard 2003). Depending on the disease severity and method of disease induction, demyelinating or axonal features would predominate. Adoptive transfer of P2-reactive T cell lines in Lewis rats led to EAN that was characterized by axonal dysfunction or degeneration with minimal demyelination, whereas adoptive transfer of myelin-sensitized lymph node cells (T cells and B cells) led to prominent demyelinating features (Taylor and Pollard 2003).

Conduction failure in EAN and AIDP often precedes the onset of demyelination and is attributed to paranodal retraction and disruption of nodal sodium (Na) channels (Lonigro and Devaux 2009; Novakovic et al. 1998). Interestingly, the disruption of nodal Na channels and paranodal alterations are preceded by disappearance of adhesion molecules neurofascin186 and gliomedin thought to be mediated by Abs against these proteins. These findings are seen only in EAN induced by immunization with peripheral myelin, not in EAN induced by P2 (Lonigro and Devaux 2009). Subsequent studies reveal that immunization with gliomedin, but not with neurofascin, induces a progressive neuropathy that is characterized by nodal disruption and demyelination (Devaux 2012). These observations support the concept that potential antigenic targets in GBS and CIDP are not limited to peripheral myelin proteins and may include nodal proteins. The caveat is the low frequency of immunoglobulin G (IgG) Abs against neurofascin, gliomedin, or contactin in sera of patients with AIDP or CIDP (Devaux et al. 2012; Ng et al. 2012). This issue is not unique to nodal proteins because T cell or humoral responses to myelin proteins also occur with variable frequency in AIDP and CIDP (Sanvito et al. 2009; Yan et al. 2001). Thus, the major culpit antigen(s) implicated in AIDP and CIDP remain elusive at this time, although disease heterogeneity or low assay sensitivity may be contributing factors.

Acute Autoimmune Neuropathy Models Mediated by Abs against Glycolipids

The first clue that glycolipids may be an immune target in inflammatory neuropathies originates from the work by Nagai' s group and Saida's group in the 1970s, when they succeeded in the induction of neuritis with gangliosides and galactocerebroside (Galc) in rabbits, respectively (Nagai et al. 1976; Saida et al. 1979). Galc-induced neuritis is Ab mediated because intraneural injection of serum from immunized animals would cause myelin vesiculation, macrophage infiltration, and focal demyelination (Saida et al. 1978). Conduction block was observed in single ventral root nerve fibers upon topical application of anti-Galc serum (Lafontaine et al. 1982).

Approximately two decades later, animal models of ataxic sensory neuropathy and AMAN were established by immunization studies with gangliosides such as GD1b and GM1, respectively (Kusunoki et al. 1996; Yuki et al. 2001). The clinical manifestations of Abs against gangliosides correlate with ganglioside localization in the PNS. For example, GQ1b is preferentially localized to cranial nerves III, IV, and VI and to dorsal root ganglia (DRG), whereas GM1 is predominantly found in ventral roots and some DRGs. GD1b and GT1 are highly expressed by DRG (Willison and Yuki 2002). Therefore, it is not surprising that immunization of rabbits with purified GD1b would result in ataxic sensory neuropathy characterized by degeneration of dorsal roots with preservation of sciatic motor conduction parameters (Kusunoki et al. 1996). This is accompanied by downregulation of TrkC and apoptosis of DRG neurons (Takada et al. 2008).

The rabbit AMAN model induced by ganglioside mixture or purified GM1 is characterized by flaccid limb paralysis

associated with high titers of GM1 IgG Ab, Wallerian-like degeneration, and lack of lymphocytic infiltration (Yuki et al. 2001). Moreover, there is deposition of IgG and complement products as well as disruption of Na(v) channel clusters and paranodal axoglial junctions in the nerves or nerve roots, which might lead to conduction block, although eventually axonal degeneration occurs (Susuki et al. 2007). In general, it is difficult to transfer disease to mice, even with intraperitoneal implantation of hybridoma cells secreting antiganglioside Abs, which resulted in a mild patchy axonal neuropathy (Sheikh et al. 2004). The susceptibility to develop antiganglioside neuropathies is influenced by ganglioside density, as demonstrated by passive transfer of anti-GD1a Ab into GD3s$^{-/-}$ mice (which overexpress GM1 and GD1a; Goodfellow et al. 2005). Distal nodes of Ranvier in intramuscular motor nerve bundles are also targeted by anti-GD1a Abs, resulting in the loss of Na^+ channel staining, and loss of perineural currents. Complement activation products, including membrane attack complex, were found at the lesion site. The loss of Na^+ channel staining can be prevented by complement and calpain inhibition, but calpain inhibition is insufficient to restore perineural currents (McGonigal et al. 2010). Taken together, findings from these experimental models would explain the spectrum of axonal involvement in human AMAN, which can range from reversible conduction failure associated with rapid recovery to axonal degeneration associated with poor outcome.

Aside from the nodes of Ranvier, the presynaptic component of the neuromuscular junction is another vulnerable site for antiganglioside-mediated injury (Plomp and Willison 2009). In vitro studies on phrenic nerve–diaphragm preparation reveal that anti-GQ1b Abs cause a complement-dependent "α-latrotoxin-like effect" characterized by initial dramatic increase in the frequency of miniature endplate potentials followed by calpain-mediated synaptic necrosis and neuromuscular transmission failure (Halstead et al. 2004; Plomp et al. 1999). In the murine model of Miller Fisher syndrome, mice were injected with CGM3, an immunoglobulin M (IgM) Ab that reacts with GQ1b, GD3, and GT1a, and then 16 hours later by normal human serum (Halstead et al. 2008). The latter was required to observe functional defects in mice. In this model, the feasibility of targeting the complement system with eculizumab, a humanized monoclonal Ab that blocks the formation of C5a and C5b-9, was demonstrated by positive findings of protection against respiratory paralysis from a transmission defect at the diaphragm neuromuscular junction (Halstead et al. 2008). Undoubtedly, the progress in identifying glycolipids as antigens has made a significant impact on our understanding of GBS and other dysimmune neuropathies.

Animal Models of Ab-Mediated Chronic Dysimmune Neuropathies

Aside from CIDP, chronic dysimmune neuropathies include anti-myelin-associated glycoprotein (MAG) neuropathy, multifocal motor neuropathy (MMN) mediated by anti-GM1 IgM Ab, and other paraproteinemic neuropathies. We will focus on anti-MAG neuropathy and MMN here. Anti-MAG neuropathy is characterized by gradual onset of numbness, sensory ataxia, and distal weakness and by distal demyelination on nerve conduction studies (Dalakas 2010; Kaku et al. 1994; Latov et al. 1988). The antigenic determinant resides in the carbohydrate moiety of the MAG molecule, and the monoclonal IgM also recognizes sulfoglucuronyl glycosphingolipid, a PNS-specific glycolipid (Ilyas et al. 1984; Van den Berg et al. 1996). The pathogenic role of anti-MAG Abs was demonstrated by intraneural injection of sera from patients with anti-MAG neuropathy into feline or rabbit sciatic nerves or by their passive transfer into chicks (Hays et al. 1987; Monaco et al. 1995; Tatum 1993). Myelin alterations such as vesiculation and widely spaced myelin induced by intraneural injection of anti-MAG Ab are complement dependent (Monaco et al. 1995). In the chick model, there is also myelin splitting and deposition of IgM on the outer myelin lamellae similar to that observed in human anti-MAG neuropathy. Immunization of cats with purified sulfoglucuronyl glycosphingolipid induces an ataxic neuropathy characterized by lymphocytic infiltrates in the dorsal root ganglia, although no overt abnormalities are found in nerve roots or nerves (Ilyas et al. 2008).

In contrast with anti-MAG neuropathy, MMN is an asymmetric motor neuropathy that occurs more frequent in males, often starting in upper limbs. Additional features include conduction blocks when stimulating motor nerves and presence of IgM Abs to GM1, and less frequently to asialo-GM1, GD1a, or GM2. There are MMN patients who have conduction block but are seronegative for anti-GM1 Abs. On the other hand, there are also seropositive MMN patients without conduction block. The inability to detect conduction block is attributed to its location (e.g., nerve root level) or lack of sensitivity of electrophysiologic criteria used for defining conduction block (Muley and Parry 2012; Vlam et al. 2012). Although specific animal models of MMN are not available, anti-GM1 IgM Abs have been shown to trigger complement activation in vitro and, therefore, can potentially disrupt the nodes of Ranvier, paranodal junctions, and presynaptic terminals, in a manner similar to that induced by antiganglioside IgG Abs (Piepers et al. 2010; Yuki et al. 2011). Intraneural injection of sera from patients with MMN causes reduction of amplitude and temporal dispersion in rat tibial nerves (Uncini et al. 1993). Direct application or passive transfer of MMN plasma has been shown to attenuate distal nerve conduction in the mouse phrenic nerve–diaphragm preparation (Roberts et al. 1995). MMN sera may contain Abs to other antigens, such as NS6S heparin disaccharide, although additional studies are required (Pestronk et al. 2010). The use of combinatorial glycoarray or enzyme-linked immunosorbent assay will increase the sensitivity of antiglycolipid testing in MMN, particularly with anti-GM1/Galc complexes (Galban-Horcajo et al. 2013).

Experimental Autoimmune Autonomic Ganglionopathy

Autoimmune autonomic neuropathy or ganglionopathy usually presents as a subacute, monophasic illness characterized by pandysautonomia and positive Abs to ganglionic nicotinic acetylcholine receptors (AChRs). It was later recognized that Abs to ganglionic AChRs can be detected in some patients with chronic autoimmune autonomic neuropathy or ganglionopathy as well (Klein et al. 2003). Immunization of rabbits with recombinant α3 subunit (aa1-205) results in impaired pupillary reaction to light, gastrointestinal hypomotility, distended bladders, and impaired neurotransmission through abdominal sympathetic ganglia. The severity of dysautonomia correlates with the levels of antiganglionic AChR Abs (Lennon et al. 2003). Histologically and ultrastructurally, superior cervical ganglia appear normal in experimental autoimmune autonomic ganglionopathy, although neuronal density is slightly lower than in control rabbits (Tajzoy et al. 2011). Passive transfer studies with IgG from rabbit experimental autoimmune autonomic ganglionopathy or IgG from human autoimmune autonomic neuropathy or ganglionopathy reproduce the autonomic dysfunction in mice with maximal deficits at 3 to 5 days after single intraperitoneal injection, and recovery by 10 to14 days after injection (Vernino et al. 2004). Autonomic neuropathy may be autoimmune or paraneoplastic in origin. Support for the latter is demonstrated by the expression of ganglionic AChRs in small cell lung carcinomas (SCLC; Lennon et al. 2003).

Paraneoplastic Sensory Neuronopathy

The anti-Hu paraneoplastic syndrome, which often precedes the detection of a malignancy, is characterized by sensory neuronopathy and encephalomyelitis, and by Abs directed against a group of RNA-binding proteins, HuR, HeN1, HuC, and HuD. Only HuC and HuD are expressed in both neurons and tumors such as SCLC (Antic and Keene 1997). Anti-Hu Ab, also known as antineuronal nuclear antibody1 (ANNA-1), does not appear to play a crucial role in the pathogenesis of the disease. The disease cannot be reproduced in animals by immunization with HuD or by passive transfer of anti-Hu Abs, which also cannot kill neurons in vitro (Sillevis Smitt et al. 1996; Tanaka et al. 2004). In a mouse model of SCLC induced by conditional inactivation of tumor suppressor cell genes Rb1 and Trp53, 14% of animals exhibited anti-Hu Ab response. Although no obvious clinical signs of neurologic dysfunction were found, the study did not include electrophysiology or histological evaluations of dorsal root ganglia or brain tissues (Kazarian et al. 2009).

The failure to establish an animal model mediated by anti-Hu Abs suggests other pathogenetic mechanisms are at play. Bien and colleagues (2012) reported higher CD8/CD3 ratio and more frequent apposition of granzyme B^+ cytotoxic T cells to neurons in brain tissues from anti-Hu cases compared with cases with Abs against N-methyl-D-aspartate receptors or potassium channels. These findings support the concept of T cell–mediated neurodegeneration in paraneoplastic syndromes with onconeural Abs directed against intracellular antigens, in contrast with those paraneoplastic syndromes mediated by pathogenic Abs directed against surface antigens (such as calcium channel Abs in Lambert Eaton syndrome).

Spontaneous Autoimmune Polyneuropathy

Nonobese Diabetic Mouse Model

Induced animal models are useful for investigating whether a putative antigen fulfills Witebsky's postulate of autoimmunity, although the adjuvant-supported protocols are rather artificial. Most human autoimmune diseases occur spontaneously in genetically susceptible individuals, albeit with some exogenous triggers that are often unknown or not easily identified. Factors that determine the predilection of certain tissues to autoimmune disease and the course of disease are poorly understood. Spontaneous autoimmunity can develop in inbred rodent strains or in animals genetically manipulated to increase their susceptibility to autoimmune diseases. A prominent naturally occurring model of spontaneous organ-specific autoimmunity is the nonobese diabetic (NOD) mouse, which expresses an unusual $H\text{-}2^{g7}$ MHC haplotype that is associated with increased susceptibility to type 1 diabetes, thyroiditis, sialadenitis, gastritis, and also autoimmune neuropathy under certain conditions (Anderson and Bluestone 2005).

Disease manifestations in NOD mice can vary, depending on the cytokine and costimulatory milieu, which regulates the balance between pathogenic and regulatory T cells (Tregs; Bour-Jordan et al. 2004; Setoguchi et al. 2005). Treatment with anti–interleukin 2 Ab leads to depletion of Tregs with early onset diabetes, neuropathy, and other autoimmune diseases (Setoguchi et al. 2005). In contrast, elimination of a costimulatory molecule B7-2 (CD86) in NOD mice leads to protection against diabetes mellitus but triggers the onset of a spontaneous autoimmune polyneuropathy (SAP) at 6 to 7 months of age. SAP mimics CIDP (progressive form) in many aspects, including disease course, electrophysiologic and histologic features of demyelination, and axonal loss (Kim et al. 2009; Salomon et al. 2001; Ubogu et al. 2012).

The B7-1/B7-2–CD28/CTLA4 pathway is critical to the regulation of lymphocyte activation and homeostasis of Tregs. Signaling by CD28 promotes T cell activation, whereas signaling by CTLA-4 downregulates T cell responses (Freeman et al. 1993; Ledbetter et al. 1990). In contrast, both receptors are required for optimal generation and function of $CD4^+$ Tregs (Salomon et al. 2000; Wing et al. 2008). In B7-2 KO NOD mice, B7-1 is increased in $CD11b^+$ and $CD11c^+$ cells infiltrating SAP nerves (Salomon et al. 2001). Interestingly, there is also a preferential upregulation of B7-1

in CIDP nerves (Kiefer et al. 2000). Yet, SAP in B7-2 KO NOD mice is accelerated by B7-1 blockade (Bour-Jordan et al. 2004). Thus, the requirement for B7-1 for activation of myelin-reactive T cells can be bypassed in the absence of functional Treg compartment.

We and other investigators found that SAP in B7-2 KO NOD mice is mediated by interferon γ (IFN-γ)–secreting Th1 cells that are reactive against myelin P0, and at least 2 pathogenic P0 epitopes are involved, P0 (1–25) and P0 (180–199; Bour-Jordan et al. 2005; Kim et al. 2008; Louvet et al. 2009). P0 is an Aire-regulated tissue-specific self-antigen in the thymus. Aire-deficient mice have increased autoreactivity against P0 and develop autoimmune neuropathy that is mediated by IFN-γ similar to that observed in B7-2 KO NOD mice (Su et al. 2012). Interestingly, there is an additive effect of B7-2 deficiency and Aire deficiency on the development of autoimmune neuropathy. Blockade of both B7-1 and B7-2 also induced a fulminant, early onset neuropathy in Aire-deficient NOD mice due to severely decreased frequency of Tregs (Zeng et al. 2013).

Aside from T cells, sera from SAP mice contain Abs to P0, which may contribute to peripheral nerve injury (Kim et al. 2008; Yan et al. 2001). We have recently found that depletion of B cells and plasmablasts with anti-CD19 Ab led to the attenuation of SAP (Abraham et al. 2013). Note that P0 is expressed not only in the PNS myelin but also by peri-islet Schwann cells, suggesting a potential mechanism linking the islet and PNS autoimmunity (Kim et al. 2008). The shift from islet to PNS autoimmunity is also observed in intercellular adhesion molecule 1 (ICAM-1)–deficient NOD mice and is due to altered costimulation rather than loss of adhesive activity of ICAM-1. These mice exhibit Th17 bias instead of Th1 bias (Horste et al. 2010).

Another pathway that is important in the development of autoimmune neuropathies is the PD-L1–PD-1 pathway. PD-L1 deficiency enhances inflammation in the chronic constriction injury model (Uceyler et al. 2010). NOD mice with antidiabetogenic haplotype (H-2^b) and PD-1 deficiency (NOD. *H2^b-Pdcd1$^{-/-}$)* develop sialadenitis, gastritis, and autoimmune neuropathy (Yoshida et al. 2008). In contrast with B7-2 KO NOD mice, there is enhanced expression of B7-2 and CTLA-4 in the nerves of NOD.*H2^b-Pdcd1$^{-/-}$* mice (Yoshida et al. 2008). Thus, neuritogenic T cells can be generated in the context of H-2^{g7} or H-2^b and in the presence or absence of B7-2.

There is a growing list of genes that influence the susceptibility to autoimmune disease, but the disease manifestations may vary depending on the type of perturbation. Just as in NOD mice, it is not uncommon to find different autoimmune diseases in the same family. Therapy directed against an immune molecule sometimes triggers another autoimmune disease. The NOD mouse model allows one to study the mechanisms underlying the shift from one autoimmune disease to another upon alteration of costimulatory or cytokine milieu or upon administration of target-specific immunotherapy.

Other Models of SAP

There are a few other interesting models of SAP. Transgenic mice expressing the MHC class II IA^b molecule that presents a single peptide Eα52-68 develop inflammatory neuropathy mediated by CD4$^+$ T cells at 10 weeks or older (Oono et al. 2001). In contrast with B7-2 KO NOD mice in which the incidence of neuropathy is higher in females than males, no sex difference was found in the study of Oono and colleagues. The expression level of MHC-self peptide complexes on thymic dendritic cells contributes to the development of organ-specific autoimmunity in that lower expression leads to incomplete negative thymocyte selection (Oono et al. 2001).

A FasL-dependent, macrophage-mediated demyelinating polyneuropathy has also been reported in transgenic C57BL/6 mice overexpressing IL-10 under the control of human *VMD2* promoter. *VMD2* encodes bestrophin, which is highly expressed in retinal pigment epithelium, nervous system, and testes. Systemic levels of IL-10 did not change, but increased expression of IL-10 was found in the eye, sciatic nerve, spinal cord, and brain of symptomatic transgenic mice (Dace et al. 2009). Yet, the disease was restricted to the PNS, similar to B7-2 KO NOD mice. The mechanisms underlying the predilection for certain tissues are poorly understood, but they may be partly related to the local microenvironment and a lesser ability of the blood nerve barrier than blood brain barrier to impede the access of lymphocytes to the tissues. Sciatic nerve sections from symptomatic mice showed increased expression of IL-12, IFN-γ, FasL, and ICAM (Dace et al. 2009). Thus, overexpression of IL-10 triggers or exacerbates inflammation, even though it acts as an anti-inflammatory cytokine at normal levels. Interestingly, both B7-2 KO NOD mice and VMD2-IL10 transgenic mice were originally generated to study other diseases, namely, type 1 diabetes and Best vitelliform macular dystrophy, respectively.

Inflammatory neuropathy has also been observed in other species. The so-called coonhound paralysis was observed in black and tan coonhounds, which developed polyradiculoneuritis 7 to 14 days after being bitten by a raccoon (Cummings et al. 1982). In spite of suspicion for infectious etiology, attempts to isolate a virus from raccoon saliva have not been successful. The other entity is the acute canine idiopathic polyneuropathy, which shares features with coonhound paralysis except for lack of exposure to raccoon saliva. Intraneural injection of serum from dogs with acute canine idiopathic polyneuropathy induced demyelination of sciatic nerves of male wistar rats, although anti-Galc Abs were not significantly higher in acute canine idiopathic polyneuropathy than control serum (Brown et al. 1985).

Role of Immune System in Animal Models of Inherited Neuropathies

Inherited neuropathies are caused by defects in several culprit genes, including myelin components P0, PMP22, and

gap junction protein connexin32 (Reilly et al. 2011). The first clue that the immune system plays a role in inherited neuropathies comes from the identification of $CD8^+$ T lymphocytes and macrophages within the endoneurium of $P0^{+/-}$ mouse mutants (Shy et al. 1997). Crossbreeding of these mutants with mice deficient in lymphocytes (RAG-$1^{-/-}$) led to attenuation of the demyelinating phenotype, which can be reversed by bone marrow transfer from wild-type mice (Maurer et al. 2001; Schmid et al. 2000). Subsequent crossbreeding of $P0^{+/-}$ mutant with mice deficient in macrophage colony stimulating factor revealed that macrophages are actively involved in demyelination (Carenini et al. 2001). The same findings extend to other models of hereditary neuropathy, such as connexin32 KO mice, and some PMP22 mutants (Kobsar et al. 2003; Kobsar et al. 2005). Note that $P0^{+/-}$ mice have been shown to have lower thymic P0 transcript, causing impaired central tolerance to P0 and enhanced susceptibility to EAN-induced by P0 (180–199; Miyamoto et al. 2003).

$P0^{+/-}$ mice and connexin32 KO mice are characterized by normal myelin formation during the first 3 months followed by slowly progressive neuropathy. In contrast, homozygous P0 KO mice have abnormal myelination early on (dysmyelination) with substantial loss of axons. In these mutants, the location, recruitment, and phagocytic behavior of macrophages in the nerves appear to differ from those observed in $P0^{+/-}$ mice. RAG-1 deficiency unexpectedly led to enhanced axonal loss in P0 KO mice, suggesting a net neuroprotective effect of T lymphocytes on axon survival (Berghoff et al. 2005). The exact mechanisms remain to be elucidated, although activated T lymphocytes have been shown to produce brain-derived neurotrophic factor and other growth factors (Kerschensteiner et al. 1999; Linker et al. 2010). The important role of immune reactions is supported by reports of coexistence of inherited neuropathy and inflammatory neuropathy, with some patients responding to immunosuppressants (Ginsberg et al. 2004; Malandrini et al. 1999; Mazzeo et al. 2012).

Conclusions

Animal models of autoimmune neuropathy have allowed investigators to investigate the pathogenicity of PNS-reactive T cells and autoAbs against PNS antigens and to study immunoregulatory mechanisms pertinent to disease development. These experimental models also facilitate the development and testing of novel therapeutic strategies. For example, disease severity in both EAN and SAP is attenuated by treatment with a sphingosine 1 phosphate (S1P) receptor modulator FTY720, a sphingosine 1 phosphate receptor modulator that regulates lymphocyte trafficking (Kim et al. 2009; Zhang et al. 2008). Selective immunoadsorption and complement inhibitors are likely to benefit Ab-mediated neuropathies more than other inflammatory neuropathies (Halstead et al. 2008; Townson et al. 2007). We have come a long way in our understanding of GBS, CIDP, and other inflammatory neuropathies, although some mysteries remain to be unraveled. The availability of various transgenic or KO mice provides opportunities to investigate the complex interactions of genetic and immunologic factors in the development of autoimmune neuropathies.

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