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Minireview: Autoimmune Responses to Myelin Proteolipid Protein*

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The authors present a brief historical sketch of the development of our understanding of immune responses to myelin proteolipid protein (PLP) and the acceptance of PLP as a potent antigen in the induction of experimental allergic encephalomyelitis (EAE). The distinct characteristics of the PLP molecule that may contribute to complex immune responses to this protein are reviewed and these responses are compared with those to MBP, both in the pathology of EAE and at the level of the T cell. Recent evidence demonstrating differences between T cell responses to PLP and MBP is reviewed. Finally, the potential contribution of immune responses to PLP in human diseases, particularly mutiple sclerosis (MS), that have been identified to date are then summarized.

KEY WORDS: Autoimmunity; experimental allergic encephalomyelitis; multiple sclerosis; myelin proteolipid protein

I. PLP *is* Encephalitogenic

The ability of certain brain components to induce encephalomyelitis has been recognized since the 1890s when Louis Pasteur injected humans with his rabies vaccine, which consisted of homogenized brain from infected animals, and found that a small number of his patients developed an encephalomyelopathy (1). Subsequently, Remlinger demonstrated that this was due to the brain components in the vaccine and not to the virus (2). In an attempt to reproduce this effect in experimental animals, Rivers and Schwentker injected monkeys repeatedly for approximately a year with homogenized central nervous system (CNS) tissue and produced encephalomyelitis (3). However, it wasn't until the development of Freund's adjuvant that the reproducible production of an acute form of experimental "allergic" encephalomyelitis (EAE) in animals could be achieved (4). Within a short time period, many investigators began to study EAE, with a major focus on the identification of the specific CNS tissue components which are encephalitogenic. Because white matter was more encephalitogenic than gray matter and neonatal CNS tissue

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*Special issue dedicated to Dr. Marjorie B. Lees.
For the authors to write a review on PLP and its role in EAE without Marjorie is like their sailing a ship without a captain, compass or rudder. This review is largely based on work and ideas generated in Marjorie's laboratory, but it was prepared without her input. Consequently, it lacks her meticulous reflection on the structure of each of its sentences and on the use of each word. Papers written with Marjorie are usually honed to near perfection late into the evening at her kitchen table in Newton, where food, ideas, and warmth abound, and where her very patient and accommodating husband Sidney and a demanding but lovable canine are close at hand. Writing this essay gave the authors a chance to recognize our scientific forebears, to consider where we are at this point and to contemplate our future directions in studying immune responses to PLP. We are, indeed, very grateful and indebted to Marjorie for her generous personal and scientific support, wise guidance, inspiration, strength, energy and, most importantly, friendship. Marjorie, we thank you, you are our role model, and we affectionately anticipate many more years of continued collaboration with you.

Abbreviations used in this paper: CNS, central nervous system; EAE, experimental allergic encephalomyelitis; MBP, myelin basic protein; MHC, major histocompatibility complex; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; PLP, myelin proteolipid protein; PNS, peripheral nervous system; TcR, T cell receptor

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which contains little or no myelin was inactive, the active encephalitogenic component was presumed to be a myelin constituent.

Proteolipid protein (PLP) was unknown and unnamed until 1951, when Folch and Lees coined the term to describe a group of substances that are soluble in chloroform-methanol and insoluble in water or salt solutions (5). These proteolipid proteins were found in a number of tissues, but the most abundant was that in myelin. Subsequently, Olitsky and Tal (6), Goldstein et al. (7), and Waksman et al. (8) all demonstrated that the distribution of encephalitogenic activity in myelin preparations was consistent with the hypothesis that PLP is an encephalitogen, in that all fractions of myelin that induced EAE contained proteolipids. Additional support came from studies demonstrating that when the proteolipids in total lipid extract were gradually destroyed by repeated drying, a corresponding decrease in the encephalitogenicity was observed (9).

At that time, however, it was assumed that CNS tissue would contain only a single encephalitogenic substance. Therefore, when Kies et al. demonstrated in 1956 that the residue remaining from bovine spinal cord exhaustively extracted with organic solvents could induce more severe EAE more reproducibly than the proteolipid-containing fraction (10), the general opinion was turned away from PLP as an encephalitogen. For many years thereafter, myelin basic protein (MBP) was considered to be the only encephalitogen and investigators focussed their attention on the role of MPB in EAE and in MS (11). This emphasis was in part attributable to the fundamental differences in the biochemical properties of MBP and PLP. MPB is a hydrophilic, highly charged protein and is relatively easier than PLP to isolate, purify and study.

In the early 1980s, methods allowing better purification of PLP were developed and there was a resurgence of interest in PLP as an encephalitogen. Using highly purified PLP preparations, EAE was induced in guinea pigs (12,13), rabbits (14-17), rats (18) and mice (19,20). Concerns regarding the purity of the PLP preparations and the possibility that trace amounts of MBP were present in them were, however, still voiced at this time. Because of its charges, MBP is a "sticky" protein and tends to adhere to surfaces; PLP tends to aggregate irreversibly. Thus, it was difficult to absolutely rule out the possibility that PLP could trap MBP or its peptide fragments. The demonstration that T lymphocyte lines that were specific for PLP and did not crossreact with MPB were able to induce and transfer EAE in mice (21,22) went some way towards dispelling concerns over MBP contamination. However, the demonstration by Tuohy et al. in 1988 that a synthetic peptide corresponding to a PLP sequence, which had no homology with MBP, could incude EAE in mice finally resulted in the wide acceptance of the potent encephalitogenicity of PLP (23,24). Since then, numerous additional encephalitogenic epitopes of PLP have been identified in various strains of mice and other experimental animals (Table I, Fig. 1).

II. PLP is Distinct from other Myelin Proteins

PLP is an integral hydrophobic membrane protein which contains both positively and negatively-charged regions and which spans the oligodendrocyte membrane several times. Thus, PLP differs from other myelin components which are localized on the exterior of the membrane, e.g. galactocerebroside, on the cytoplasmic face, e.g. MBP, or are not within compact myelin, e.g. myelin-oligodendrocyte glycoprotein (MOG). Various models have been advanced for the orientation of PLP, but the functions and the localization within compact CNS myelin of the different regions of PLP are not now known. PLP also differs from MBP in its distribution, as it is largely confined to the CNS, whereas MBP is abundant in the peripheral nervous system (PNS) as well as the CNS. Because of these distinct biochemical and topographical features, the functions of the various domains of PLP within myelin likely differ from those of other myelin components. Furthermore, the distinct domains of PLP could provoke diverse immune responses, i.e. responses that differ both from those to other myelin epitopes, as well as among the various PLP epitopes themselves.

All of the encephalitogenic epitopes of PLP identified to date are within the regions of PLP that are proposed to be extramembranous, i.e. either on the extracellular or cytoplasmic faces of the oligodendrocyte membrane (Fig. 1). One possible explanation for this is that the hydrophobicity of the peptides in the membrane-spanning regions would make them difficult to dissolve in any substance suitable for injection into experimental animals, and undissolved peptides may not induce immune responses as efficiently as solubilized peptides do. Indeed, it has been our experience with the encephalitogenic PLP peptide 178-191, which is moderately hydrophobic, that if an undissolved form in water is used for immunization, the proportion of mice that develop EAE and the severity of the disease are dramatically decreased. It is possible that extremely hydrophobic membrane spanning regions of the PLP molecule cannot be easily processed by antigen-presenting cells and, therefore, are not presented to T cells. Thus, the local-

Table I. Encephalitogenic Epitopes of Myelin PLP in Experimental Animals

PLP Residues	Sequence	Strain/Species	Reference
43-64	EKLIETYFSKNYQDYEYLINVI	PL/J (H-2^u) mouse	(26)
43-64	EKLIETYFSKNYQDYEYLINVI	NOD[1] (H-2^{nod}) mouse	(27)
56-70	DYEYLINVIHAFQYV	Biozzi AB/H (H-2^{dql}) mouse	(27)
91-110	YTTGAVRQIFGDYKKTTICGK	NZ/W rabbit	(28)
103-116	YKTTICGKGLSATV	SWR (H-2^q) mouse	(23,29)
104-117	KTTICGKGLSATVT	SJL (H-2^s) mouse	(30)
139-151	HCLGKWLGHPDKF	SJL (H-2^s) mouse	(29,31)
178-191	NTWTTCQSIAFPSK	SJL (H-2^s) mouse	(32)
215-232	PGKVCGSNLLSICKTAEF	C3H (H-2^k) mouse	(33)
217-244	KVCGSNLLSICKTAEFQMTFHLFIAAFV	Lewis (Rtl^l) Rat[2]	

[1]Non-obese diabetic
[2]W. F. Hickey, personal communicaton

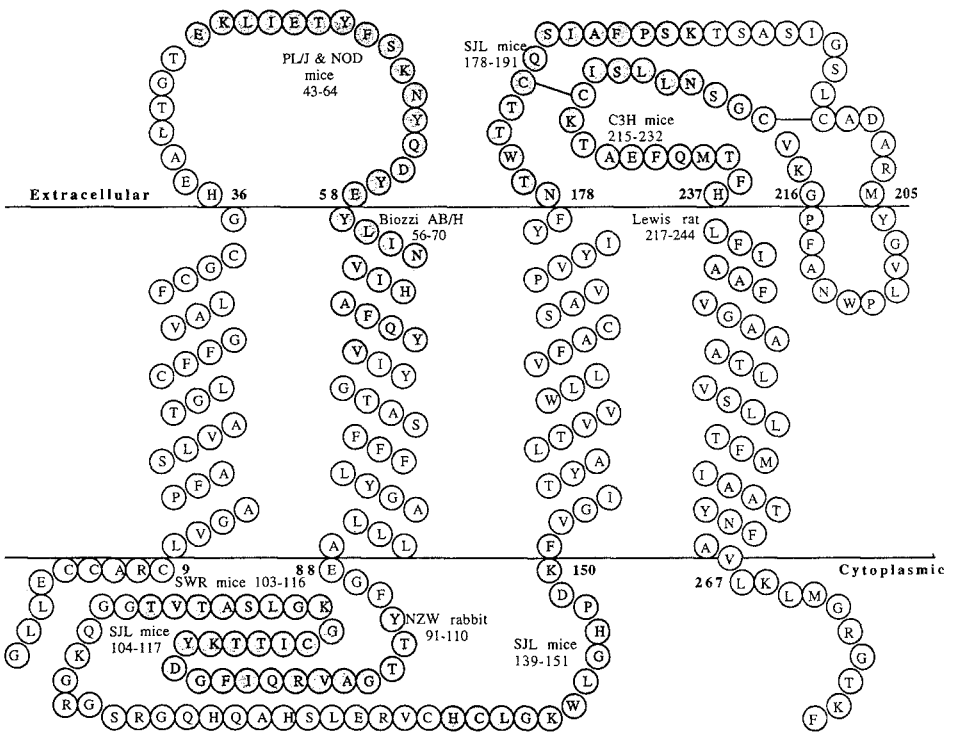

Fig. 1. Encephalitogenic epitopes of PLP in a model of PLP orientation based on that of Lees and Bizzozero (25).

ization and intrinsic biochemical characteristics of PLP, as well as the other myelin epitopes, may profoundly affect the nature of the immune responses they incite. In addition, epitopes on the external face of myelin might be more accessible to immune-mediated damage by either cellular or humoral mechanisms whereas epitopes on the cytoplasmic face could be less accessible.

III. Differences Between T cell Responses to PLP and to MBP

Once PLP had been conclusively demonstrated to be an encephalitogen, it was expected that it would be immunologically similar to MBP. However, immune responses to PLP appear to be more complex than those to MBP. In each murine strain thus far studied, there is

a single dominant epitope of MBP that most of the reactive T cells recognize. By contrast, when the whole PLP molecule is injected into mice, there is a strong response to multiple peptides (32). Analyses of the T cell receptors (TcR) of T cell clones specific for encephalitogenic determinants of MBP in mice, rats and humans have demonstrated a restricted TcR V β usage. Even in SJL mice, where nested epitopes within the encephalitogenic peptide MBP 89-101 sequence have been suggested, about 50% of the encephalitogenic T cell clones responding to this peptide utilize the same TcR V β gene segment (34). Furthermore, both mouse and rat MBP-specific encephalitogenic T cell clones use the same V α and V β gene families, even though the T cells in these rodents recognize different major histocompatibility complex (MHC) class II molecules and different MBP fragments. Since TcR usage is generally thought to be related to the recognition of the antigen-MHC complex, it is somewhat surprising that encephalitogenic T cells use the same V region genes in the absence of similarities in antigen specificity. Based on observations on MBP-induced EAE, Heber-Katz and Acha-Orbea advanced the "V-region disease hypothesis", in which it was suggested that the TcR of a given disease defines the disease rather than the antigen/MHC complex it recognizes (35). If this hypothesis is correct, specific therapies based on V gene usage could be of immense value. Indeed, *MBP-induced* EAE has been prevented or reversed by treatment of rodents with anti-TcRV β antibodies and peptide reagents (36). We are, however, unaware of analogous studies in PLP-induced EAE. Nevertheless, TcR usage of autoreactive T cells has been shown to be restricted in many autoimmune diseases and this restriction is now considered to be a "hallmark" of autoreactivity.

If encephalitogenic T cells are selected for a disease-related nervous system antigen, irrespective of the antigen/MHC combination used to expand the T cell population, one might predict similarities in TcR usage of PLP-reactive T cell clones as seen in MBP-reactive T cells. To address this question, we made T cell lines and clones to various encephalitogenic determinants of PLP in SJL mice (37), and analyzed TcR usage by PLP peptide 139-151-specific T cell clones. Of five PLP peptide-specific T cell clones analyzed by cDNA cloning, five different V βs and four different V αs were found to be used by these clones in association with different TcR J β and J α chains (38). This indicates that there is much greater diversity in TcR gene usage than there is in MBP responses. In addition and in further contrast to data on MBP responses, three different encephalitogenic PLP determinants studied thus far in mice with three different MHC (H-2) haplotypes show considerable diversity in the TcR repertoire. Overall, these results suggest that the V region hypothesis may not be applicable to immune responses to PLP.

Differences between the limited TcR usage in the response to MBP and the heterogeneous usage in responses to PLP could have important biological implications in that they may affect *susceptibility* to EAE induced by these two myelin autoantigens. We hypothesized that since T cells using many different TcR respond to PLP whereas those responding to MBP use fewer TcR, changes or limitations in the naive TcR repertoire might affect the ability of MBP, but not PLP to induce EAE. To test this, we studied EAE susceptibility in TcR V β chain transgenic SJL mice, in which greater than 95% of the T cells express the TcR V β 8.2 which is normally deleted in SJL mice. The resultant skewing of the TcR repertoire prevented susceptibility to EAE induced by immunization with MBP, but not with PLP (38, manuscript in press). This suggests that immune responses to PLP peptides can be generated through the use of a wide range of TcR, including TcR V β 8.2, i.e. there is considerable plasticity in the response to PLP. By contrast, immune responses to MBP are more restricted as a consequence of the more rigid requirements of the TcR. These results demonstrate *for the first time* that there are *unequivocal differences* in immune responses to MBP and PLP.

Recruitment of a restricted TcR repertoire could be due to deletion in the thymus of the majority of the autoreactive T cells resulting in the seeding of only a limited type or number of autoreactive T cells (so-called "forbidden clones") into the periphery. This probably is the case with MBP, since MBP has been found in the thymus at an early stage of development (39). We postulate that the greater diversity in autoimmune responses to PLP may be due to a lack of thymic deletion to PLP resulting from the general restriction of PLP to CNS myelin, to its later appearance in CNS tissues than MBP, and its apparent lack of expression in the early developing thymus. Thus, the differences between the immune responses to PLP and MBP might be related to physico-chemical differences between the two molecules (see II, above), to their different tissue distribution, or their possibily different times of appearance in CNS development (see Discussion in paper by Kinney et al., this issue), any or all of which could affect the adult T cell repertoire.

IV. PLP-Induced EAE and Its Implications for MS

In the models of EAE induced by PLP and by PLP peptide-specific T cell clones that have been studied in detail, the clinical, pathological, and immunopathological features of the disease are very similar, if not iden-

tical to those induced with whole CNS tissue or MBP sensitization (17,40,41). Furthermore, adhesion molecules and cytokines play critical roles in the activation and encephalitogenicity of PLP peptide-specific T cell clones, as they do for MBP peptide-specific T cell clones (42,43). In these models, inflammatory infiltrates and the associated demyelination are limited to the CNS with sparing (as is generally the case in MS) of the PNS. These distinct patterns of localization are evident in spinal nerve root entry zones in which the inflammatory infiltrates stop abruptly at the border between the CNS and PNS myelin (Figure 2). Within the CNS, more inflammation is generally found in the heavily myelinated CNS white matter than in the gray matter, although this is not exclusive in either EAE or MS. The gross anatomic distribution of lesions in the various PLP peptide-induced mouse EAE models (as in MS) is somewhat variable. For example, spinal cord lesions are more prevalent in the SJL mouse model whereas there is a greater tendency for lesions to be localized in the periventricular cerebral hemispheres in other mouse strains, and subtle differences in the clinical manifestations of the disease might result from these differences in lesion location. Thus, the actual microanatomic localization of the target antigen(s) may dictate the distribution of inflammatory/demyelinating lesions, whereas widely diffusible substances, e.g. cytokines, may have less of a localizing effect in the inflammatory response. If autoimmune responses to PLP or other myelin antigens play pathogenetic roles in MS, there could be as yet unidentified antigenic differences in myelin among different anatomic regions of the human CNS that may account both for the preferential localization of MS lesions to the optic nerves, periventricular white matter, and (in some forms) the spinal cord. Indeed, cellular immune reactivities to PLP as well as MBP have been demonstrated in some MS patients, (44-46) but relationships of these responses to the cause, clinical manifestations, or lesion distribution in MS have not been established.

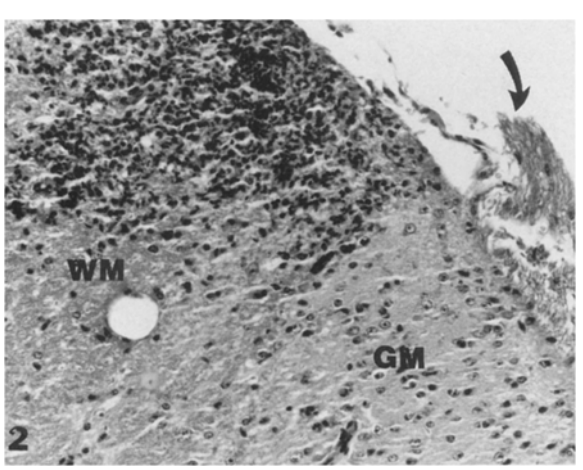

Fig. 2. Perivascular mononuclear cell and neutrophil infiltrate in the white matter (WM), but not gray matter (GM) or proximal spinal nerve root (arrow) of an SJL mouse with acute EAE induced by sensitization with a synthetic peptide corresponding to PLP peptide 178-191.

In animals with EAE, antibodies to various myelin components, including PLP are found in the serum and cerebrospinal fluid (16,47,48), but precise correlations between antibody levels and degree of histologic demyelination are not apparent. Recently, it has been shown that an immunodominant B cell epitope is on the carboxyl terminus of PLP (49), a region which Konola et al. found to be on the cytoplasmic face of myelin (50). Earlier studies suggested that anti-PLP antibodies do not cause demyelination in vitro (51), but antibodies to specific PLP domains have not been systematically examined in EAE. Patients with MS often have antibody responses to MBP and other myelin components (52,53) and immunoglobulin-producing cells and plasma protein deposits are found in active lesions. To date, however, definitive pathologic roles for antibodies to PLP or any other myelin components have not been established in either EAE or MS.

V. Appreciating the Limitations of Disease Models and the Implications for Other Human Demyelinating Diseases and Autoimmunity

A major step in the evolution of our understanding of demyelinating diseases has been the recognition (attributable in large part to Marjorie's persistent efforts on PLP) that MBP is likely not the only myelin autoantigen involved in either EAE or MS. Indeed, MOG has recently been shown to be encephalitogenic (54) and immune responses to it (55) as well as other myelin components could also be involved in MS. A historical perspective on Marjorie's career illustrates the point that a far-reaching conclusion based, for example on an EAE model in a single species or strain (or on a single molecule such as MBP) will likely prove to be an oversimplification and, perhaps, of uncertain relevance to human disease.

Marjorie's career provides a clear demonstration of the inestimable value of basic research. Initially unanticipated insights into a variety of neurological diseases have arisen from an understanding of basic cellular and molecular processes, i.e. the induction of immune responses to PLP. In addition to their possible pathoge-

netic roles in MS, immune responses to PLP may be relevant to other myelin diseases. For example, adrenoleukodystrophy is also characterized by marked inflammatory infiltrates in the CNS white matter, suggesting the presence of an anti-myelin immune response (56). The complexity of the immune response to PLP in comparison to MBP may have also have broader implications for autoimmune responses, both within and outside of the nervous system, in which dominant epitopes are not readily evident and in which TcR gene usage may not be restricted.

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