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MS AS AUTOIMMUNE DISEASE: MYELIN ANTIGENS

W. Fierz

Section of Clinical Immunology, University Hospital, Zurich (Switzerland)

Ever since autoimmunity was considered to play a decisive role in the pathogenesis of MS, the search for the responsible antigens was one of the main domains in MS research, and still is. Nevertheless, in contrast to the situation in experimental models of the disease, where there has emerged a gradually increasing wealth of information about the nature of antigens involved, we still are virtually ignorant about antigens in MS. We are not even sure whether such entities as MS antigens do exist. On the other hand, the ever more detailed analysis of antigens in experimental allergic encephalomyelitis (EAE) has helped immensely not only to identify possible candidates for MS antigens, but, perhaps more importantly, to elucidate the pathogenic mechanisms of autoimmunity.

The identification of antigens in EAE followed a more-or-less straightforward logical path from crude brain and spinal cord homogenate to myelin, and from there to the purified myelin proteins, proteolipid protein (PLP) and myelin basic protein (MBP). PLP is the major structural protein of brain white matter accounting for more than 50 % of the central myelin membrane protein.

Its highly hydrophobic nature has resisted biochemical characterization for a long time. Recently, the entire amino acid sequence of bovine PLP has been determined and two different models have been proposed for its conformation in the myelin membrane [1, 2]. The 276-residue-long polypeptide chain contains at least three hydrophilic segments that are orientated towards the extracytosolic site. Early claims of PLP being encephalitogenic [3] have always been questioned because of possible contamination by MBP. Recent studies, however, in which EAE was induced in mice with PLP-specific T-cell lines that were unreactive to MBP have unambiguously demonstrated the encephalitogenicity of PLP and its apoprotein DM-20, which is identical to PLP except for a deletion of residues 116-150 [4].

MBP, on the other hand, was always the preferred antigen in EAE studies, probably because of its better solubility. MBP of various species has been studied extensively with regard to its biochemistry and EAE-inducing capacity, and various encephalitogenic sites in MBP have been identified that differ from species to species (for review see [5, 6]). The 170-residue-long (bovine) polypeptide that contributes to about 30 % of central myelin structural proteins, has no extracytosolic segments and therefore the immune system can only have access to it when it is freed from its cellular confinement. Although it is known that MBP-like material and fragments thereof are found in various body fluids like CSF, blood and urine, ramification of this MBP metabolism with regard to its antigenicity is not yet fully understood. The question could well be related to another poorly understood problem, *i.e.*, why MBP-induced EAE is largely confined to the CNS although MBP also contributes to the integral myelin proteins of the PNS.

Further development in the molecular characterization of these antigens was then intricately interconnected with advances in the study of T-cell immunology which brought new insights into the nature of cellular and humoral mechanisms of autoimmune responses. These advances have revealed three major complexities: 1) the MHC-dependence of T-cell antigens, 2) possible cross-reactivity to viral antigens, and 3) the interaction between responses to T-cell antigens and B-cell antigens.

T-cell antigens.

It is now clear that the prototype of a T-cell antigen is a peptide of 10- to 20-amino-acid length, whereas B-cell antigens very often are epitopes defined by the 3-dimensional conformation of the whole protein, and they may also be of non-protein character. The peptide nature of T-cell antigens has its counterpart in the peptide-binding property of MHC molecules that are expressed on the cell surface of the antigen-presenting cells (APC). APC are responsible for processing the proteins into peptides that are then recognized by the T cells in context with the presenting MHC molecules. This MHC-restricted recognition, however, makes the definition of a T-cell antigen dependent on the MHC-type of the immune system involved. To give an example, T cells of an H-2^s mouse recognize different peptides of MBP than T cells of an H-2^u mouse (table I). Similarly, T cells of Lewis (LEW) rats (RT1^l) recognize different MBP epitopes than T cells of Brown Norway (BN) rats (RT1^n). This MHC control has formally been proven by using the congenic strains LEW.1N (BN MHC on LEW background) that dit not show a T-cell response to p68-88, and BN.B1 (LEW MHC on BN background) that did respond to p68-88 [7].

Whilst this MHC-controlled antigen recognition by T cells seems to be unambiguous in inbred animals, the situation becomes more complex in hybrid animals. The T-cell response to an epitope restricted by one parental MHC haplotype might become dominant over the response to an epitope restricted to the other parental MHC haplotype. A further complication in hybrid animals can ensue from the possibility that a T-cell response to an antigen in context with self-MHC may cross-react with a foreign MHC-type. It has been obser-

TABLE I. — **T-cell antigens in EAE.**

Species	Strain	MHC	Epitopes	Ref.
			MBP	
Guinea pig	13		114-122	[29]
Rat	LEW	$RT1^l$	68-88, 72-84	[30, 31]
	PVG	$RT1^c$	68-88	[30]
	F334	$RT1^{lvl}$	68-88	[30]
	BN	$RT1^n$	43-67	[9]
	BN.B1	$RT1^l$	68-88	[7]
Mouse	SJL/J	$H\text{-}2^s$	89-169	[32]
	SJL/J	$H\text{-}2^s$	89-101	[33]
	SJL/J	$H\text{-}2^s$	87-98, 91-104	[34]
	PL/J	$H\text{-}2^u$	1-11	[35]
	B10.PL	$H\text{-}2^u$	1-9NAc	[36]
			PLP	
Mouse	SJL/J	$H\text{-}2^s$	major PLP	[4]
	SJL/J	$H\text{-}2^s$	DM-20	[4]
	SWR	$H\text{-}2^q$	103-116	[37]

ved, *e.g.* in SJL mice, that T cells specific to MBP/$H\text{-}2^s$ can cross-react to $H\text{-}2^k$ [8]. Such a cross-reaction may modulate the T-cell response to that epitope in ($H\text{-}2^s \times H\text{-}2^k$)F1 hybrid animals.

In parallel with the property of myelin proteins and peptides to be recognized by T cells, usually goes the capacity of the antigens to induce EAE, since EAE is primarily a T-cell-mediated disease. There might be exceptions, however, as it is known, for example, that a T-cell response in a (LEW × BN)F1 animal to the BN-type epitope of MBP p43-67 is, for unknown reasons, less encephalitogenic than the T-cell response to the LEW-type epitope p68-88 [9]. T-cell responses to other epitopes might not even be encephalitogenic at all, and more importantly, might protect the animal from the disease. These questions are the subject of current research projects and it has, recently been found, for example, that oral tolerization of LEW rats against EAE by feeding the animals MBP is more pronounced in animals fed with the non-encephalitogenic peptides p1-37 or p90-120 than in animals fed with the encephalitogenic peptide p44-89 [10].

Whilst such MHC-dependent mechanisms are highly interesting with regard to the pathogenesis of the disease and possible immunospecific therapeutic intervention, they make it extremely difficult to identify antigens in an outbred population like humans. One has to expect that in MS patients with different HLA haplotypes, the T-cell repertoire of brain or viral proteins is different and that the relative dominance between non-encephalitogenic and encephalitogenic epitopes is again dependent on both parental HLA haplotypes.

Studies aimed at detection of either PLP- or MBP-specific T-cells in MS patients have produced conflicting results. Antigen-specific stimulation of T cells in bulk cultures usually showed only marginal stimulation indices and have not produced convincing data for cellular immunity to either PLP or MBP in MS. Recently, 57 T-cell clones deri

ved from postmortem MS brain plaque tissue were not reactive to either PLP or MBP, nor were 235 clones derived from CSF and 126 clones from the peripheral blood of other MS patients [11]. In other studies, MBP-specific T-cell lines and clones were established from the peripheral blood of three MS patients [12], but also from six out of nine normal healthy individuals [13]. From one patient, T-cell clones have been developed that reacted against either the C-terminal half or the N-terminal half of human MBP [14]. However, the role of PLP- or MBP-specific T cells in the pathogenesis of MS remains unclear.

In addition to the variability imposed on the antigenicity of proteins by the MHC haplotypes, it is conceivable that the polymorphism of the genes that code for the T-cell antigen receptor conveys further complexity to antigen recognition. At any rate, the influence of MHC and non-MHC genes on the antigen repertoire of T cells and the regulation of their putative encephalitogenicity is very likely the reason for the well-known association of MS susceptibility to HLA-DR, and perhaps to certain alleles of the T-cell receptor genes.

Cross-reaction to viral antigens.

A further consequence of the peptide nature of T-cell antigens is the possible cross-reactivity with viral peptides. The shorter the epitope recognized by the T cells, the higher the probability that an analogous sequence is found in some viral proteins that might be the target of cross-reactions. Interestingly, as this mimicry hypothesis concerns pathogenic mechanisms, one has to bear in mind that T cells are able to detect single amino acid substitutions in a short peptide and, consequently, one probably has to look for identical sequences over the length of about 10 amino acids. The longest mimicry sites in PLP reported so far have been 5 consecutive identical amino acids or 7 residues, when allowing for one mismatch [15]. In MBP, several mimicry sites of 4 or 6 consecutive identities, respectively, have been found [16]. Of course we do not yet know which of these sites might be encephalitogenic in humans. On the other hand, a sequence of 6 amino acids (p69-74) was found in the encephalitogenic site for rabbits that was identical to a site in hepatitis B virus polymerase, and rabbits immunized with the virus peptide showed small cellular CNS infiltrates [17].

B-cell antigens.

The refinement of EAE models by using purified myelin proteins instead of brain or spinal cord homogenate as antigens, has allowed the identification of MBP- and PLP-specific T cells as the disease-inducing agents. On the other hand, this development, which culminated in disease induction by peptide-specific T-cell clones, profoundly changed the pathology of the disease, at least in the rat model. The major change was the loss of demyelination and it was soon suspected that B-cell antigens were additionally needed to produce the complete picture of demyelinating EAE [23].

Recently, this suspicion has been corroborated by experiments in which the combination of a low dose of MBP-specific T-cells with monoclonal antibodies to a myelin-oligodendroglial glycoprotein (MOG) transferred into naive recipient animals led to a demyelinating EAE that very closely resembles the pathology of MS [18-20]. MOG is a 51-kDa glycoprotein located on the surface of CNS myelin sheaths and oligodendrocytes [21]. The same anti-MOG antibodies seem to occur in correlation with disease activity in guinea pig EAE induced by spinal cord homogenate [22]. Whether antibodies to other myelin antigens could produce a similar effect is under current investigation. Anti-galactocerebroside monoclonals seemed at first to have a similar effect [20], but later experiments could not corroborate these findings. It is not yet clear, however, how far the IgG subclass of the monoclonals used determines the results. At any rate, circum-

stantial evidence for a demyelinating effect of anti-glycolipids in EAE has been collected for some time [23, 24], and direct evidence for demyelinating activity of galactocerebroside antiserum *in vivo* has been described by three groups [25-27].

Again in MS patients, the finding of anti-myelin antibodies is not conclusive as to their pathogenic significance. Various studies have shown the presence of antibodies in CSF against glycolipids and MBP, but it is not yet clear which of these antibodies contribute to the demyelinating process or prevent (or stimulate) remyelination. Nevertheless, at least the anti-MBP antibodies seem to correlate with disease activity [28], which gives them some importance even if they only turn out to represent an epiphenomenon of the underlying demyelinating process.

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MULTIPLE SCLEROSIS AS AUTOIMMUNE DISEASE: VASCULAR ANTIGENS

N.H. Sternberger

Department of Neurology, The School of Medicine, University of Maryland, 22, South Greene Street, Baltimore, MD 21201 (USA)

Brain endothelial cells form a specialized barrier which executes a variety of functions, including exclusion of cells and many substances from the brain [2, 8] and mediated transport of nutrients and peptides [6]. This barrier may be modified after interaction with specifically sensitized lymphocytes and endothelial cells induced to express class II major histocompatibility complex Ia molecules [10, 17]. Although it is recognized that endothelial cells play an essential role in immune responses, the molecular specializations and alterations that these cells undergo in relation to an immune function, such as permitting the entry of inflammatory cells into the brain, are just beginning to be studied.

Several recent studies of experimental allergic encephalomyelitis (EAE) in guinea pigs have demonstrated alterations in vascular antigens. Kato and Nakamura [5] examined the endothelial localization of magnesium ion-dependent adenosine triphosphatase (Mg^{2+}-ATPase) in various stages of EAE. Mg^{2+}-ATPase was cytochemically observed in vesicles and on the abluminal surface of endothelia. In the acute stage of disease, Mg^{2+}-ATPase was also found on the luminal surface of endothelia of affected blood vessels. Betz *et al.* [1] proposed that there is an asymmetric distribution (polarity) of transporters and that the luminal and abluminal membranes of endothelial cells are functionally unique. The altered polarity of Mg^{2+}-ATPase distribution in EAE suggests that cellular metabolism is affected in "EAE" endothelia.

A potential role for endothelial cell fibronectin, along with fibrin/fibrinogen, in monocyte attachment and facilitated migration of inflammatory cells has been suggested by Sobel *et al.* [11, 12]. In these studies, the cellular expression and extracellular deposition of fibronectin was examined in guinea pig acute EAE. Fibronectin is synthesized by many cells, including endothelia and macrophages, and is localized on the luminal surface of only a few brain blood vessels in normal animals [9]. The number of vessels reacting with a monoclonal antibody to fibronectin increased in sensitized guinea pig central nervous system prior to and during acute disease. Extracellular deposits of