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EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS MEDIATED BY T LYMPHOCYTE LINES: GENOTYPE OF ANTIGEN-PRESENTING CELLS INFLUENCES IMMUNODOMINANT EPITOPE OF BASIC PROTEIN[1]

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Lewis rats are susceptible to experimental autoimmune encephalomyelitis (EAE), and their T lymphocytes recognize epitopes in the 68-88 sequence of guinea pig myelin basic protein (BP). BN rats are resistant to EAE, and their T lymphocytes recognize epitopes outside of the 68-88 sequence, probably in the 43-67 portion of BP. To investigate the influence of the genome of antigen-presenting cells (APC) on the dominance of BP epitopes for T lymphocyte lines, we selected anti-BP lines from (Lewis × BN)F_1 rats by using the APC of Lewis, BN, or F_1 origin. We now report that the F_1/Lewis and F_1/F_1 lines recognized the 68-88 epitopes and were highly encephalitogenic in F_1 rats, whereas the F_1/BN line recognized the 43-67 epitopes and was only weakly encephalitogenic. Thus, the genotype of the APC can influence the immunologic dominance for T lymphocytes of BP epitopes, and this dominance in turn can influence the expression of disease.

Experimental autoimmune encephalomyelitis (EAE)[3] can be induced in genetically susceptible animals by immunizing them to the basic protein of myelin (BP), a chemically defined self-antigen (1). A study of various aspects of EAE has been facilitated by the use of long-term lines of rat T lymphocytes specifically reactive to BP that are functionally active in producing EAE or in vaccinating against the disease (2, 3).

The immunodominant epitope (or epitopes) for Lewis rat anti-BP T lymphocyte lines was found to be in the 68-88 peptide sequence of BP, whereas the immunodominant epitope (or epitopes) for Brown Norway (BN) rat anti-BP T lymphocyte lines was located outside of that peptide, probably in the 43-67 sequence (4). The identification of different epitopes by T lymphocytes of Lewis and BN rats could be important functionally because Lewis rats are highly susceptible to EAE, whereas BN rats are highly resistant (5). We therefore sought to determine whether resistance or susceptibility was due to the immunodominance of different epitopes in these strains, and whether genes expressed in antigen-presenting cells (APC) influenced epitope dominance. Our strategy was to use whole BP to raise T lymphocyte lines from (Lewis × BN)F_1 rats. APC of F_1, Lewis, or BN origin were used along with whole BP in the selection culture. After the establishment of stable lines, we tested the fine specificity of each line to BP peptides to learn whether the APC genotype could influence the identity of the immunodominant epitopes. To investigate the clinical consequences of epitope immunodominance, we inoculated rats with the various lines. The results indicate that the genome of the APC can influence the immunologic dominance of BP epitopes, and epitope immunodominance in turn influences the capacity of the T lymphocytes to produce disease.

MATERIALS AND METHODS

Rats. Inbred Lewis (RT1-l), BN (RT1-n), and (Lewis × BN)F_1 hybrid rats were supplied from the Animal Breeding Center of the Weizmann Institute. Rats were used at 2 to 3 mo of age and were matched for sex in each experiment.

Antigens. BP was prepared as described by Hirschfeld et al. (6) from spinal cords of guinea pigs without the step of purification by column chromatography. BP-peptides were prepared and were purified as described (7). Concanavalin A (Con A) was purchased from Miles-Yeda (Rehovot, Israel), and purified protein derivative of tuberculin (PPD) was purchased from Statens Serum Institute (Copenhagen, Denmark).

Immunization of animals. EAE was induced in rats by injecting each hind footpad with 0.05 ml of an emulsion of 25 μg/ml BP in phosphate-buffered saline (PBS) emulsified with an equal volume of complete Freund's adjuvant (CFA) containing 100 μg/ml *Mycobacterium tuberculosis* H37Ra (Difco Laboratories, Detroit, MI). On day 9 after immunization, the draining lymph nodes were removed, and the cells were pooled. Suspensions of lymph node cells were prepared and were assayed directly for their in vitro proliferative response to antigens, or were submitted to the selection of antigen-specific lines as described (3). Other rats were observed for the development of EAE.

Proliferative response of lymphocytes from primed rats. Lymph node cells were seeded in flat-bottomed microtiter plates (Costar, Cambridge, MA) in triplicate wells (8). Each well contained 1×10^6 lymph node cells in 0.2 ml culture medium, with antigens in the optimal concentrations determined by dose-response experiments (BP at 50 μg/ml, and PPD at 25 μg/ml). Con A was used at 1.2 μg/ml. Proliferation culture medium was composed of Dulbecco's modification of Eagle's medium supplemented with 2-mercaptoethanol (5×10^{-5} M), L-glutamine (1 mM), antibiotics, sodium pyruvate (1 mM), nonessential amino acids (1% of ×100), and 1% fresh autologous serum. The cultures were incubated for 72 hr at 37°C in humidified air plus 7.5% CO_2. Each well was pulsed with 1 μCi of [^{3}H]thymidine (specific activity, 46 Ci/mmol; Nuclear Research, Negev, Israel) for the final 18 hr. The cultures were harvested on fiberglass filters by a multiharvester, and incorporation of [^{3}H]thymidine was measured in a liquid scintillation counter. The proliferative response was

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[3] Abbreviations used in this paper: BN, Brown Norway; BP, basic protein; EAE, experimental autoimmune encephalomyelitis.

expressed as cpm.

Selection and maintenance of lines. Lines of lymphocytes reactive against BP were developed (3, 9) from suspensions of lymphoid cells by cultivating the cells in supplemented Eagle's medium for 72 hr at a concentration of 5×10^6/ml in 60 mm Petri dishes (Falcon Plastics, Oxnard, CA), with 6 ml/dish of BP (60 μg/ml). The lymphocytes were then seeded at a concentration of 2×10^5/ml in propagation medium. The propagation medium was the proliferative medium described above minus autologous serum and supplemented with 15% (v/v) of supernatant of Con A-stimulated lymphocytes as a source for T cell growth factor prepared as described (3), and 10% horse serum (GIBCO, Grand Island, NY). The cultures were transferred every 3 to 4 days until the next restimulation. The cells (2×10^5/ml) were then incubated for 3 days with BP (10 μg/ml) in the presence of irradiated (1500 rad) syngeneic or semi-syngeneic thymus cells (15×10^6/ml) as accessory cells.

Proliferative response of T cell lines. The method to determine proliferative responses of T cell lines to various antigens was similar to that described for cells from primed rats, except that each culture well contained 2.5×10^4 line cells plus 10^6 accessory cells in the form of irradiated thymus cells unless indicated otherwise (3). Concentrations of antigen or mitogen used were BP, 10 μg/ml; BP peptides, 1 μg/ml; PPD, 12.5 μg/ml; and Con A, 1.2 μg/ml. After 24 hr of incubation, each well was pulsed with [^{3}H]thymidine for an additional 18 hr, and the wells were harvested and were counted.

Mediation of EAE. After antigenic restimulation, the line lymphocytes were collected and were washed, and 5×10^6 to 10×10^6 in 1 ml PBS were injected i.v. into rats. The recipients were observed daily for development of EAE (3, 10). Rats were scored for typical signs of EAE according to the method of Coates et al. (11): flaccid tail = 1, hindleg weakness = 2, hindleg paralysis = 3, and moribund state = 4.

RESULTS

Syngeneic APC and proliferation of BN and Lewis anti-BP lines. The importance of the genotype of APC in the proliferative responses of anti-BP T lymphocyte lines can be seen in Table I. Lines specifically directed to BP could be raised both from EAE-susceptible Lewis and from EAE-resistant BN strains of rats. However, the lines originating from each strain responded only to BP associated with syngeneic APC. There was no response to the control antigen PPD, irrespective of the origin of the APC.

Different BP peptides are recognized by Lewis and BN anti-BP lines. To define better the BP epitopes recognized by the Lewis and BN lines, each line was incubated with whole BP or peptide fragments of BP in the presence of syngeneic APC. Table II illustrates that each line recognized different epitopes of BP (4). The entire response of the Lewis line to whole BP could be accounted for by its response to the 68-88 peptide or to the 43-88 peptide that included the 66-88 sequence. The BN line, although it responded to the 43-88 peptide, showed no response to the 66-88 peptide. Its response to the 43-67 peptide was strong, but less than that demonstrated to whole BP or to the 43-88 peptide. Therefore, the BP line probably recognized epitopes in the 43-67 part of BP that may need the 68-88 sequence for native conformation. Be that as it may, the BN line recognized epitopes outside of the 68-88 sequence, which is the immunodominant peptide for Lewis T lymphocytes.

TABLE I

Syngeneic APC required for proliferative responses of Lewis and BN anti-BP lines[a]

Anti-BP Line	APC	Proliferative Responses (cpm × 10^{-3} ± SD)		
		No antigen	PPD	BP
Lewis	Lewis	1.2 ± 1	2.3 ± 1	110 ± 10
	BN	0.9 ± 1	1.2 ± 1	0.6 ± 1
BN	Lewis	1.7 ± 1	1.8 ± 1	0.9 ± 1
	BN	2.1 ± 1	2.4 ± 1	121 ± 1

[a] Lewis or BN line lymphocytes were assayed for their response to BP, PPD, or Con A in the presence of irradiated thymus accessory cells originating from syngeneic or allogeneic rats.

EAE mediated by Lewis and BN lines. Table III shows that the ability of the anti-BP line cells to induce EAE was influenced by the genotype of the recipient rat, as well as by the identity of the line cells. Lewis anti-BP line cells mediated a high incidence of severe EAE equally well in Lewis or in F_1 rats, but not in BN rats. The BN anti-BP line, in contrast, induced a high incidence of EAE of moderate severity in BN rats, a low incidence of mild disease in F_1 rats, and was not encephalitogenic in Lewis rats. Thus it seemed that the difference in BP epitopes that were dominant for Lewis and BN T lymphocytes might account for differences in the encephalitogenicity of the different line cells. However, other explanations were possible, and it was necessary to investigate epitope dominance and encephalitogenicity by using T lymphocytes and recipients of the same genotypes.

Development of (Lewis × BN)F_1 line cells. To study the effect of APC genotype on BP epitope dominance and encephalitogenicity, we developed T lymphocyte lines from F_1 rats by using whole BP and APC of F_1, Lewis, or BN parental origin. Table IV shows that the BP-primed lymph nodes of F_1 rats responded strongly in proliferative assay in vitro to the T lymphocyte mitogen Con A and to PPD, and responded weakly to BP. From this pool of cells we raised three separate lines each using whole BP as the selecting antigen and either F_1, Lewis, or BN APC. The lines, designated respectively F_1/F_1, F_1/Lewis, and F1/BN, quickly lost their responses to PPD and responded fairly well to BP (Table IV). To investigate the haplotype restriction of the responses of the F_1 lines to BP or Con A, we assayed proliferation of the line cells in the presence of APC of parental Lewis or BN, or of F_1 origin. Table V illustrates that all three F_1 lines responded to Con A in the presence of each of the APC. In contrast, the responses to BP were influenced by the genotype of the APC. The F_1/F_1 line had a relatively weak response in the presence of BN APC, whereas the F_1/Lewis line showed no response at all to BP together with BN APC. The F_1/BN line responded to BP in the presence of BN or F_1 APC, but showed no response to BP in the presence of Lewis APC. Thus in their responses to BP, the F_1/F_1 and F_1/Lewis lines showed a preference for APC expressing

TABLE II

BP peptide specificities of Lewis and BN anti-BP lines[a]

Line Cells	Proliferative Responses (cpm × 10^{-3} ± SD)							
	No antigen	Con A	BP	BP peptides				
				1–37	43–88	43–67	68–88	89–169
Lewis	7.7 ± 1	230 ± 6	235 ± 18	9 ± 2	223 ± 7	12 ± 2	225 ± 10	5 ± 1
BN	5.6 ± 2	270 ± 10	310 ± 13	6 ± 1	300 ± 9	146 ± 71	9 ± 1	6 ± 1

[a] Lewis or BN line lymphocytes were tested for their proliferative responses to Con A, BP, or BP peptides.

TABLE III

EAE mediated by Lewis or BN T lymphocyte lines in Lewis, BN, or (Lewis × BN)F_1 recipients[a]

Line Cells Injected (5×10^6)	Recipients	EAE		
		Percent incidence	Mean day of onset	Mean clinical score (range)
Lewis	Lewis	100	4.0	4 (4)
	BN	0		0
	F_1	100	4.5	4 (4)
BN	BN	88	6.0	2 (2)
	Lewis	0		0
	F_1	22	6.5	1.5 (1–2)

[a] Line lymphocytes were restimulated by incubation with BP and then were injected i.v. into groups containing five to nine recipient rats each. The incidence and clinical score of EAE were recorded.

Lewis genes, whereas the F_1/BN line showed a preference for APC expressing BN genes.

F_1 anti-BP lines recognize different epitopes. To discover whether epitope dominance was influenced by the genotype of the APC used to select the lines, we tested the proliferative responses of the F_1 lines to whole BP and to its peptides. Figure 1 illustrates that the 68-88 peptide was dominant for the F_1/F_1 and F_1/Lewis lines, as it was for the Lewis line (Table II). The F_1/BN line (Fig. 1), in contrast, did not respond to the 68-88 peptide but showed the same specificity for the 43-67 peptide as the BN line (Table II). Thus the genotype of the APC influenced the immunodominance of the BP epitopes for F_1 anti-BP T lymphocyte lines. The Lewis-associated epitopes were in the 68-88 peptide, whereas the BN-associated epitopes were outside the 68-88 sequence, probably in the 43-67 sequence.

Haplotype restriction of epitope recognition by F_1/F_1 anti-BP line. The above results indicated that the F_1/F_1 line showed the epitope preference for the 68-88 peptide characteristic of the F_1/Lewis or parental Lewis lines. To investigate the haplotype preference of the F_1/F_1 line, we studied its proliferation to whole BP, its peptide fragments, PPD, or Con A in the presence of F_1, Lewis, or BN APC. Table VI shows that there was little or no response to PPD presented by any of the APC. In contrast, each of the APC induced a strong response to Con A. However, the responses to whole BP and to its 68-88 peptide fragment were elicited only with the use of APC of F_1 or Lewis origin. There was relatively little response of the F_1/F_1 line to BP or its peptides elicited by APC of BN origin. Thus the F_1/F_1 line showed the haplotype restrictions of its Lewis parent, just as it showed its epitope preference.

Encephalitogenicity of F_1 lines. To test the importance of epitope specificity for encephalitogenicity, we inoculated the various F_1 lines into F_1, Lewis, or BN rats and observed the development of disease. Table VII shows that the F_1/F_1 and F_1/Lewis lines induced a high incidence of marked paralysis in F_1 or in Lewis recipients. The F_1/F_1 line did not cause disease in BN recipients. This may be explained by the observation that this line did not respond well to BP presented by BN APC in vitro (Table VI). In contrast, the F_1/BN line caused a low incidence of very mild disease expressed as tail weakness in either F_1 or BN rats (Table VII). Therefore, the contribution of the APC to epitope dominance had far-reaching consequences clinically. F_1 line cells that recognized the BN-associated epitopes were poorly encephalitogenic in F_1 rats compared with the F_1 line cells that recognized the Lewis-associated 68-88 epitopes.

DISCUSSION

The results of the experiments lead to the conclusion that the identity of the immunodominant epitopes of BP preferred by T lymphocytes can be influenced by the genome of the APC. Lewis APC in the selection cultures of F_1 lymph node cells induced the emergence of a line that responded to the 68-88 peptide, whereas BN APC induced a line that lost its ability to respond to the 68-88 peptide, but responded to epitopes in the 43-67 portion of the 43-88 sequence (Fig. 1). Thus, each parental APC seemed to favor clones of F_1 lymphocytes responsive to BP epitopes characteristic of the parental Lewis or BN strains (Table II). The association between immune response genotype and epitope dominance has been known for some time (12); however, the unique feature of this study is the demonstration of the clinical consequences of this association.

It has been proposed that the effects of APC genotype on epitope dominance result from "holes" (the absence of T lymphocytes with receptors for a particular epitope associated with certain major histocompatibility complex (MHC) allelic products; 13) in the T lymphocyte repertoire. In other words, F_1 populations of T lymphocytes would have two types of anti-BP cells, those recognizing the 68-88 epitope associated with Lewis APC, and those recognizing the 43-67 epitope associated with BN APC exclusively. However, we have previously demonstrated that a Lewis T lymphocyte line can be generated to the 43-67 peptide by using Lewis APC (4), so there is no absolute "hole" in the repertoire.

The APC themselves could select one or another epitope by genetically controlled differential metabolism of the BP molecule (14). However, studies of molecular events in the processing of avidin, another antigen under genetic control, have failed to reveal genetic differences in antigen processing (15).

A third idea is that the APC presentation of antigen to T lymphocytes involves the physical association between antigen and MHC gene product, and that this association can hinder or advance the accessibility of particular epi-

TABLE IV

Antigen specificity of responses of primed lymph node cells and anti-BP line cells from (Lewis × BN)F_1 rats[a]

T Lymphocytes	Line Selecting APC	Proliferative Response (cpm × 10^{-3} ± SD)			
		No antigen	BP	PPD	Con A
Primed lymph node	—	21 ± 4	38.5 ± 1.6	127 ± 28	421 ± 32
F_1/Lewis	Lewis	11 ± 2	66 ± 12	9 ± 06	89 ± 10
F_1/BN	BN	2 ± 0.2	23 ± 1	2 ± 0.9	83 ± 1
F_1/F_1	(Lewis × BN)F_1	2 ± 0.4	25 ± 0.6	8 ± 1.6	64 ± 2

[a] The proliferative responses of primed lymph node lymphocytes obtained from (Lewis × BN)F_1 rats were measured without added accessory cells.

TABLE V

APC haplotype preference of F_1 line response to BP[a]

Line Cells	APC in Stimulation	Proliferative Response (cpm × 10^{-3} ± SD)		
		No antigen	BP	Con A
F_1/F_1	None	0.1 ± 0.02	0.2 ± 0.05	1.4 ± 0.1
	F_1	0.3 ± 0.1	27 ± 2	91 ± 7
	Lewis	0.2 ± 0.02	16 ± 2	58 ± 7
	BN	0.15 ± 0.02	7 ± 0.05	57 ± 0.9
F_1/Lewis	None	0.8 ± 0.3	0.7 ± 0.03	1 ± 0.05
	F_1	1.2 ± 0.2	45 ± 2	69 ± 5
	Lewis	2 ± 0.2	54 ± 2	57 ± 9
	BN	0.7 ± 0.05	0.6 ± 0.1	20 ± 2
F_1/BN	None	0.25 ± 0.03	0.3 ± 0.07	2.5 ± 0.5
	F_1	0.5 ± 0.05	28.5 ± 0.6	25 ± 3
	Lewis	0.5 ± 0.2	0.4 ± 0.01	48 ± 7
	BN	0.6 ± 0.06	50 ± 1.5	22 ± 1

[a] F_1/F_1, F_1/Lewis, or F_1/BN line cells were assayed for their proliferative responses to BP or Con A in the presence of APC of F_1, Lewis, or BN origin.

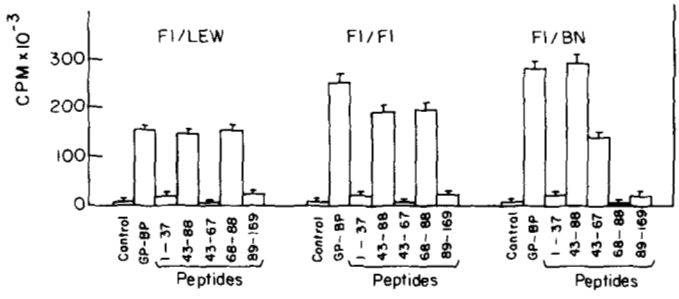

Figure 1. BP peptide specificities of F_1/Lewis, F_1/F_1, and F_1/BN lines. The proliferation assay was done by using F_1 APC.

topes (16). Different MHC allelic products might therefore provide a selective advantage to competing clones of T lymphocytes that recognize different BP epitopes (17). Be that as it may, the genome of the APC is a major factor in the determination of immunodominance of epitopes. This indicates that immunodominance is not an intrinsic property of the chemistry of the antigen but the result of the interaction of the antigen with gene products expressed in the immune system (18). The genome of the APC also appears to influence the haplotype restrictions of proliferating T lymphocytes in vitro (Table VI), and the ability of T lymphocytes to produce disease in vivo (Table VII).

Differences in EAE phenotypes between susceptible Lewis and resistant BN rats have been attributed to genes linked to the MHC (5), and differences in epitope dominance induced by Lewis and BN APC may be attributed to their MHC alleles. Whether or not MHC genes are the major factor, it is clear that the virulence of the anti-BP T lymphocyte lines was associated with their epitope specificity. The F_1 lines with Lewis (68-88) specificity produced more severe paralysis than did the F_1 line with BN (43-68) specificity (Table VII). Likewise, the Lewis line (68-88) was more virulent than the BN line (43-67) in either syngeneic or F_1 recipients (Table III). A Lewis line specific for the 43-67 peptide was not encephalitogenic (4). Hence a 68-88 epitope may serve as a more suitable target for disease than a 43-67 epitope for reasons yet unknown. In any case, this study illustrates that immunodominance and clinical disease can be divergent properties. The 68-88 epitope is a more susceptible target than the 43-67 epitope, but which of the two is immunodominant is influenced by the genotype of APC and other factors in the immune response. At present there is no evidence that contradicts the thesis that the immunodominance of BP epitopes for lines in vitro reflects the immunodominance of BP epitopes in vivo. Accordingly, BN rats might resist EAE because their immunodominant BP epitope is poorly encephalitogenic, whereas Lewis rats might be susceptible to EAE because their immunodominant BP epitope is highly encephalitogenic. It is possible but unlikely that the different epitope specificities of the anti-BP lines were unrelated to their different degrees of virulence, and all the lines with the 43-67 specificity happened by chance to have weaker effector mechanisms than did the lines with 68-88 specificity. Note that the severity of disease was defined in these studies by the degree of clinical paralysis produced by the lines. The anti-BP T lymphocyte lines do produce histologic lesions similar in general to those observed in EAE induced by active immunization, but we have not yet been able to carry out an exhaustive histologic study of the pathology produced by lines of various specificities.

Ben-Nun et al. (19) found that APC of EAE-susceptible and -resistant guinea pigs influenced greatly whether or not primed T lymphocytes responded to the encephalitogenic epitope in the nonapeptide, 114-122 sequence. The guinea pigs differed in the I region of the MHC, and therefore class II MHC gene products were probably important in the process of immunodominance. Thus this study with the use of rat T lymphocytes confirms and extends the results of previous studies that made use of primed lymph node cells of guinea pigs.

PVG rats as BN rats are resistant to induction of EAE (9). In a previous study, it was found that a highly encephalitogenic anti-BP line could be derived from PVG rats, whereas an anti-BP derived from BN rats was not encephalitogenic (9). The weakly encephalitogenic anti-BP Bn line described here was isolated independently. However, both BN lines showed the same specificity (4). Investigation of the fine specificity of the PVG anti-BP line showed that it responded to the encephalitogenic 68-88 peptide (4). Thus PVG and BN rats would appear to have different mechanisms responsible for their resistance to EAE. PVG rats seem to be capable of responding to the strongly encephalitogenic 68-88 epitope, but this

TABLE VI

Haplotype restriction of the F_1/F_1 line to the Lewis parental APC[a]

F_1/F_1 Line Stimulated with APC	Proliferative Response (cpm × 10^{-3} ± SD)							
	No antigen	PPD	Con A	BP	BP peptides			
					1–37	43–67	68–88	89–169
F_1	4.8 ± 1	7.1 ± 2	193 ± 50	64 ± 1.3	2.5 ± 0.6	4.3 ± 1	55 ± 15	5.0 ± 1
Lewis	7.6 ± 1	7.8 ± 1	105 ± 7	45 ± 5	4.6 ± 1	6.3 ± 1	35.4 ± 9	7.2 ± 1
BN	1.0 ± 0.5	2.0 ± 1	134 ± 7	6.1 ± 1	3.0 ± 0.04	4.0 ± 1	1.4 ± 0.8	2.1 ± 1

[a] F_1/F_1 line lymphocytes were assayed for their proliferative responses in the presence of APC of F_1, Lewis, or BN origin.

TABLE VII

EAE mediated by F_1 anti-BP line cells[a]

Inoculated Line Cells (5×10^6)	Recipients	EAE		
		Percent Incidence	Mean day of onset	Mean clinical score (range)
F_1/F_1	F_1	100	4	3 (3)
	Lewis	69	5	2 (2)
	BN	0		0
F_1/Lewis	F_1	100	4	3 (3)
	Lewis	90	4.5	3 (3)
F_1/BN	F_1	11	6	1 (1)
	BN	13	5.5	1 (1)

[a] F_1/F_1, F_1/Lewis, and F_1/BN line lymphocytes were restimulated by using BP in the presence of F_1 APC. The activated lymphocytes were then injected i.v. into F_1, Lewis, or BN recipients, and the incidence and clinical score of EAE was recorded. Each group contained five to 13 rats.

response is probably suppressed actively (9). In contrast to PVG rats, the genome of BN rats influences them to respond to a poorly encephalitogenic epitope. Whether or not active suppression also is involved remains to be clarified.

It is conceivable that the association of human autoimmune diseases with class II MHC alleles, serologically defined (20) or detected at the DNA level (21), may be due to processes similar to those investigated here. Class II MHC and other genes of the individual could determine which epitopes on a self antigen were dominant. If the immunodominant epitope determined by an individual's genotype happens to be a clinically pathogenic target, then the immune response might lead to disease. If the immunodominant epitope for that individual is not pathogenic, then the autoimmune response, even when induced, might be subclinical or relatively innocuous.

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