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Research Article

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T Cell Antigen Receptor V Gene Usage

Increases in Vβ8+ T Cells in Crohn's Disease

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Abstract

Crohn's disease represents part of a spectrum of inflammatory bowel diseases characterized by immune regulatory defects and genetic predisposition. T cell antigen receptor V gene usage by T lymphocytes was investigated using four MAbs specific for various V gene products. One MAb (Ti3a), reactive with Vβ8 gene products, detected increased numbers of T cells in a subset of Crohn's disease patients as compared with normal controls and ulcerative colitis patients. In family studies there was no apparent inherited predisposition to the use of Vβ8 genes, and there was no association between a restriction fragment length polymorphism of the Vβ8.1 gene and Crohn's disease. The Vβ8+ T cells were concentrated in the mesenteric lymph nodes draining the inflammatory lesions and belonged to both the CD4+ and CD8+ T cell subsets. In contrast, lamina propria and intraepithelial T cells were not enriched in Vβ8+ T cells, suggesting that these cells were participating in the afferent limb of a gut-associated immune response. The expanded Vβ8+ T cells in Crohn's disease appear to result from an immune response to an as yet unknown antigen. (*J. Clin. Invest.* 1990. 85:1770–1776.) inflammatory bowel disease • family study • RFLP • epithelial cells • cross-reactive monoclonal antibodies

Introduction

The variable regions of the T cell antigen receptor (TCRαβ)[1] are produced by productive rearrangement of gene segments: V, D, and J segments for the β chain; V and J segments for the α chain. The usage of these gene segments is thought to be a random process, although constraints on the combinations of gene segments used probably exist (1). Other selection processes involving MHC products and certain autoantigens lead to exclusion of some T cell clones during thymic maturation (2, 3). These processes have been studied primarily in the mouse, and information on the regulation of V gene usage in humans is still fragmentary.

Several MAbs to various domains of the human TCR have been characterized. Some of the MAbs detect small percentages of normal T cells and appear to be specific for certain Vβ gene products (Table I). As such they serve as useful tools to analyze Vβ gene usage by T cells in the blood or in tissue sections. In prior studies we used three such MAbs to determine V gene usage in normal donors (4) and in patients with autoimmune disorders (5). No disease-related changes in V gene usage were detected. We have now expanded these studies to include inflammatory bowel diseases (IBD). Here we report unusually high percentages of Vβ8+ T cells in a subset of patients with Crohn's disease (CD) and offer possible explanations for their presence.

Methods

Patients. PBMC were obtained from patients with the diagnosis of either CD or ulcerative colitis (UC) as defined by the criteria of Lockhart-Mummery and Morson (6). In each case, the patient's diagnosis was confirmed by histologic, radiologic, and endoscopic criteria. Mesenteric lymph nodes (MLN) were isolated from surgically resected specimens from both areas of active disease and grossly uninvolved tissue. Control tissues and lymph nodes were obtained from patients with inflammatory and noninflammatory diseases (sigmoid volvulus, diverticulitis, and colonic neoplasm at least 10 cm from disease).

Immunofluorescence. The MAbs listed in Table I have been described in detail (4, 7–9). Other MAbs used included anti-CD3 (CRL 8001; American Type Culture Collection, Rockville, MD); negative control MAb Gol 44.3 (10); a series of anti-Vβ8 MAbs including C305, IgM (11), 16G8, 2D1, and 12B8 (T Cell Sciences, Inc.); MX9; MX11; and MX12 (12). Both peripheral blood and tissue samples were used to isolate mononuclear cells and then T cells by rosetting with neuraminidase-treated sheep red blood cells (EN). Indirect staining was done with an affinity-purified goat anti-mouse Ig $F(ab')_2$ FITC reagent (Tago Inc., Burlingame, CA). Analysis by FACS with appropriate controls has been described elsewhere (4). The data are presented as percentages of positive cells normalized to the number of CD3+ T cells.

For two-color staining, cells were first incubated with MAbs to Vβ gene products, then with goat anti-mouse Ig $F(ab')_2$ FITC, saturating amounts of mouse Ig, and finally, phycoerythrin-conjugated MAbs to either CD3, CD4, or CD8. Incubations were done at room temperature for 30 min and separated by three washes.

Tissue staining. Mucosal strips were snap-frozen in TissueTek. 4-μm-thick sections were cut and stored at −70°C. Sections were stained by a biotin/avidin/peroxidase sandwich technique (Vectastain; Vector Laboratories, Inc., Burlingame, CA) using the MAbs indicated. Positive controls included anti-class I MAb W6/32, while isotype-matched MAbs were used as negative controls in each experiment.

Isolation of lymphocytes from MLN and lamina propria lymphocytes. MLNs were isolated from the mesentery of surgically resected specimens, cleared of overlying fat and vessels, and teased to a single cell suspension. T cells were purified and cultured as described below. Lamina propria lymphocytes were isolated by the method of Bull and Bookman (13) after overnight digestion of mucosal strips with colla-

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1. *Abbreviations used in this paper:* CD, Crohn's disease; EN, neuraminidase-treated sheep red blood cells; IBD, inflammatory bowel disease; MLN, mesenteric lymph nodes; RFLP, restriction fragment length polymorphism; TCR, T cell antigen receptor; UC, ulcerative colitis.

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Table I. Monoclonal Antibodies Specific for Vβ Gene Products

MAb	Specificity*	Estimated size of V gene family	References
S511 (IgG2b)	Vβ12	4	(7, 18)
C37 (IgG1)	Vβ5.3	5	(8)
OT145 (IgG1)	Vβ6.7a	9	(4, 19)
Ti3a (IgG1)	Vβ8.1, 8.2	5	(9, 17)

* For each MAb it is uncertain how many members of the indicated Vβ gene family are recognized.

genase (Worthington Biochemical Corp., Freehold, NJ), soybean trypsin inhibitor (Sigma Chemical Co., St. Louis, MO), and DNAse (type IV; Sigma Chemical Co.).

Restriction fragment length polymorphism (RFLP) analysis. A Bam HI RFLP located just upstream of the Vβ8.1 gene has been described (14). The probe used corresponds to the V region of YT35: basepairs 100–430 of the published sequence (15). DNA was isolated from EBV-transformed B cell lines of unrelated individuals, digested, and analyzed by Southern blotting as previously described (16). At high stringency, a constant band at 3 kb was observed corresponding to the Vβ8.2 gene. The Vβ8.1 gene was represented by two allelic Bam HI fragments, a 2- or 23-kb band, or both (14). The data were analyzed by the chi-square test.

Results

Peripheral blood T cells from normal volunteers and patients with UC and CD were analyzed by indirect immunofluorescence (Fig. 1, *A–D*). While MAbs to Vβ12, Vβ5, and Vβ6 gene products showed no significant disease-related differences, the Vβ8-reactive MAb Ti3a clearly identified a subpopulation of CD patients (~ 20%) with high numbers of circulating Ti3a+ T cells. In contrast, patients with UC had no significant elevations of Ti3a+ T cells as compared with the normal group.

To understand the significance of the observed elevations in Ti3a+ T cells, the clinical characteristics of those CD patients with elevated Ti3a+ T cells were analyzed (Table II). There was no correlation with disease activity, extent, location, duration, ethnic background, or therapy. The rather high incidence of fistulae (8 of 15) and associated arthritis (6 of 15) found in the patients with high Ti3a+ T cells (Table II) was compared with the incidence in CD patients without elevated Ti3a+ T cells. Incidence of fistulae was 10 of 26 ($P = 0.368$) and incidence of arthritis was 8 of 26 ($P = 0.56$). Thus, there was no significant association between the high percentages of Vβ8+ T cells and clinical characteristics of the disease.

Serial studies were performed in several patients with CD expressing high percentages of Ti3a+ cells. In general, the percentages of Ti3a+ cells remained constant, as also described with other Vβ-specific MAbs in previous studies (4, 5). However, there were some exceptions. Notably, a patient with active disease and 39% Ti3a+ T cells who underwent surgical resection of the diseased bowel segment had 3% Ti3a+ T cells 2 wk after surgery. This finding suggested a connection between disease activity and the Ti3a+ cells and raised the possibility that Ti3a+ cells might be concentrated in the affected gut tissues (see below).

One explanation for elevated Ti3a+ cells in CD is the possibility that high Vβ8 gene usage is genetically determined, possibly predisposing to the disease. This question was investigated by studying families with IBD. 12 families were studied. Eight families had more than one individual affected with IBD. In nine families, the index CD patient had elevated Ti3a+ T cells. In all but two families (Fig. 2), both unaffected and IBD relatives had normal percentages of Ti3a+ T cells. For example, in family L (Fig. 2), only one of four sisters, of which three have CD, had elevated Ti3a+ cells. Of two identical twins in family B, both with CD, only one had high Vβ8+ T cells. In contrast, in families G and B, the unaffected father of a patient with CD also had elevated Ti3a+ T cells. Neither father had any symptoms of IBD. In all 12 families (46 individ-

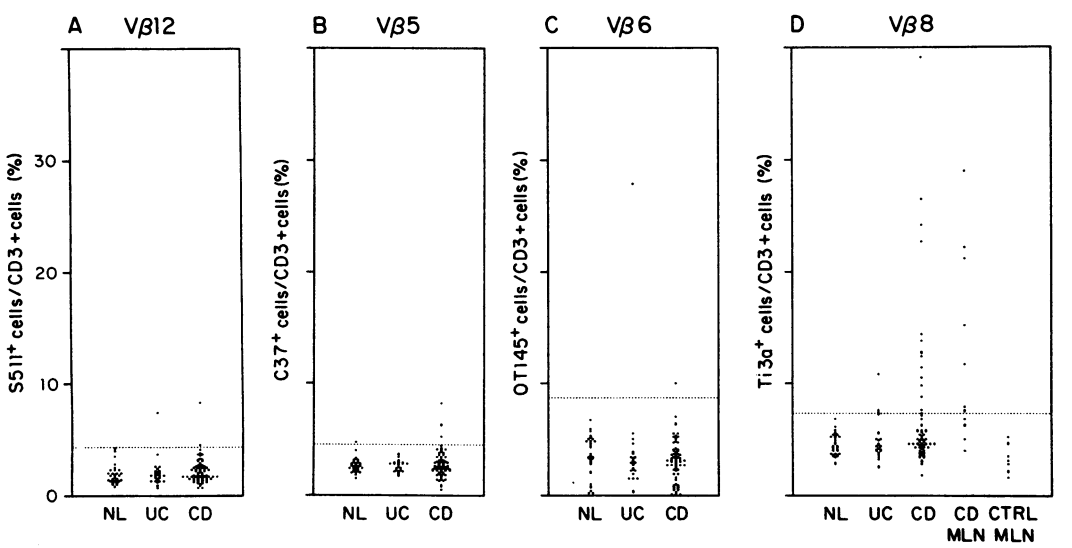

Figure 1. Percentages of positive T cells are plotted using four different MAbs to Vβ gene products: S511 (anti-Vβ12) (*A*); C37 (anti-Vβ5) (*B*); OT145 (anti-Vβ6) (*C*); and Ti3a (anti-Vβ8) (*D*). In each case, peripheral blood T cells from normal donors (*NL*) and UC or CD patients were tested. The mean + 3 SD of the NL group is indicated by a broken line (7.3% for Ti3a). For MAb Ti3a (*D*) MLN T cells were also tested from CD patients (*CD-MLN*) and controls (*CTRL-MLN*). A single patient with UC had elevated Vβ6+ T cells (*C*). Similar isolated cases have been described in other diseases (5).

Table II. Characteristics of 15 CD Patients with High Vβ8+ T Cells in the Peripheral Blood

Patient	Vβ8+	Disease location	Severity	Associated findings			Therapy	Ethnicity
				Arthritis	Fistulae	Other		
	%							
1	39.1	Recurrent ileocolitis	Pre-op, active	A	F	Abscess	Antibiotics	Jewish
2	26.5	Jejunitis	Flaring	A		Fever	Mercaptopurine	Jewish
3	24.2	Ileocolitis, status post-resection	Remission		F	Fever		Italian
4	22.7	Ileocolitis	Post-op	A				Italian
5	14.4	Ileocolitis	Flare		F		Solumedrol IV	Italian
6	13.8	Recurrent ileitis	Flare		F		Prednisone, Flagyl	Jewish
7	12.8	Ileitis, perirectal	Active	A	F		Antibiotics	Jewish
8	12.7	Colitis	Flaring	A	F		Prednisone, Flagyl, Asacol	Jewish
9	12.4	Segmental colitis	Remission			Stricture		Jewish
10	11.4	Colitis	Remission	A		Abscess	Prednisone, Flagyl	Jewish
11	10.5	Recurrent ileocolitis	Pre-op, active		F		Prednisone	Irish
12	9.8	Colitis	Moderately active			Pyoderma	Prednisone, Flagyl	Jewish
13	8.8	Ileitis, status post-resection	Remission					Irish
14	8.6	Ileocolitis	Pre-op, active		F		Asacol	Jewish
15	7.3	Ileitis	Active				Flagyl	Jewish

uals) these were the sole observations of individuals, other than the proband, with elevated Ti3a+ T cells.

Vβ8.1 and Vβ8.2, the two functional human Vβ8 genes, are located ≈ 2 kb from one another in the germline configuration (17). A polymorphic Bam HI site is located ≈ 0.5 kb upstream of Vβ8.1 in close proximity to regulatory sites for transcription of the Vβ8.1 gene (17). Thus we postulated that a major alteration in this area (such as insertion/deletion) would be linked to this RFLP and could affect Vβ8.1 gene transcription. This polymorphic Bam HI site defines 2- and 23-kb alleles. The frequencies of the heterozygous and two homozygous genotypes observed (*O*) matched the expected (*E*) frequencies in patients with CD and UC, and in normals (Table III). Therefore, no disease association with this RFLP was found. Even when only CD patients with elevated Vβ8+ T cells were analyzed, there was no association with the Bam HI RFLP. Both the family studies and these RFLP data failed to demonstrate that Vβ8 gene usage as assayed in the peripheral blood was determined by a genetic factor.

The exact localization of the Ti3a+ T cells was next investigated. In order to play a direct role in disease activity and in

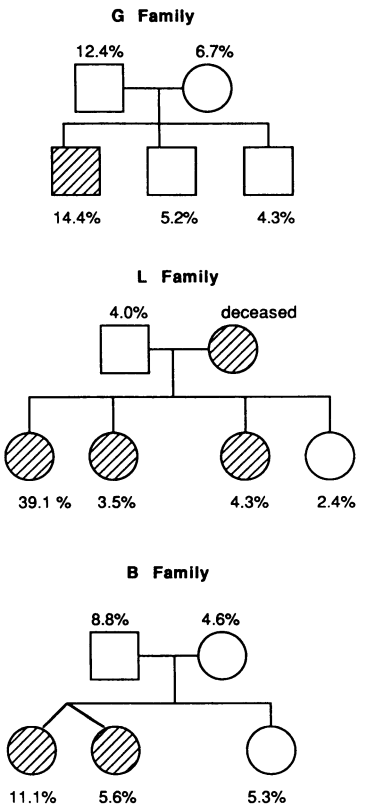

Figure 2. Family studies. Individuals with CD are hatched. The numbers refer to percentages of Ti3a+ T cells in the peripheral blood.

Table III. Bam HI RFLP of Vβ8.1 Is Not Associated with IBD

	O	*E*	χ^2
CD (n = 24)			
23/23	5	7.4	1.14
23/2	11	12.6	1.21
2/2	2	3.9	1.48
UC (n = 11)			
23/23	6	3.4	1.3
23/2	3	5.8	1.88
2/2	2	1.8	0.05
Normals (n = 20)			
23/23	6	6.2	0.08
23/2	9	10.5	0.38
2/2	5	3.3	0.44

Chi square for all observations: $\chi^2 = 7.959$; $0.1 > P > 0.05$. *O*, observed; *E*, expected.

pathogenesis, Ti3a+ T cells would have to be present locally in the lamina propria or intraepithelial space. If, on the other hand, Ti3a+ T cells were present in local lymph nodes, then it is more likely that the increase would be due to a response to a specific antigen. MLN draining diseased tissue were therefore obtained at surgery from patients with CD and from control patients with sigmoid volvulus, diverticulitis, or bowel cancer. Lymphocytes derived from teased MLN showed an increase in Vβ8+ T cells in 62% (8 of 13) of CD cases, as compared with 0% of controls (Fig. 1 *D*). This increase in Vβ8+ T cells in the MLN was therefore more striking than that found in peripheral blood and suggested an enrichment of such cells in these tissues. For example, two individuals who had normal percentages of Ti3a+ T cells in the peripheral blood showed significantly increased Vβ8+ T cells in the MLN: 3.9 (PBL)/ 11.7(MLN); 5.4/22.2. Tissue sections of MLN revealed clusters of Ti3a+ cells primarily in the interfollicular T cell–rich areas (Fig. 4 *A*). In addition, these cells were found in the EN-rosetted fraction of teased lymph nodes and not in the EN-rosette–depleted fraction. The observed increase in Vβ8+ T cells appeared to be polyclonal, being present in both CD4+ and CD8+ T cell subsets in the MLN by double fluorochrome analysis (Fig. 3). Moreover, this analysis also demonstrated that within the MLN only CD3+ T cells stained positively with the αVβ8 MAb Ti3a (Fig. 3 *B*).

In contrast to the findings in the MLN, frozen sections of diseased bowel failed to show enrichment in Ti3a+ T cells either in the lamina propria (Fig. 4 *B*) or among intraepithelial lymphocytes (data not shown). As with the other Vβ-specific MAbs listed in Table I, only small percentages of Ti3a+ cells were observed in gut mucosal specimens studied. In these studies, three to six random sections were sampled from involved mucosa in eight CD patients, four UC patients, and nine disease controls, including two patients with diverticulitis. Although it seems unlikely, we cannot rule out the possibility that focal accumulations of Ti3a+ T cells might have been missed. The finding of Ti3a+ cells enriched in the draining lymph nodes but not in the gut mucosa itself suggests that these cells may be representative of an afferent limb gut-associated immune response.

Unexpectedly, immunohistochemical stains of gut mucosa showed that MAb Ti3a cross-reacts strongly with an unidentified antigen expressed by epithelial cells (Fig. 4 *B*). This antigen was expressed on gut epithelial cells from both normal and IBD patients, and by epithelial cells from any part of the gastrointestinal tract. Moreover, freshly obtained epithelial cells from bronchial tissue, skin, and a number of epithelial cell lines derived from diverse anatomical locations also express a cross-reactive antigen. The positive epithelial cells lines included colonic epithelial cell lines (CaCo2, HT29, DLD1) and CCL13 (liver), A431 (skin), CRL 1594 (cervical carcinoma), HTB4 (bladder), HEp-2 (larynx), HTB 124 (breast), and CCL6 (small intestine). This cross-reactivity was not seen with other MAbs to TCR V gene products (S511, C37, OT145) or with control MAbs of the same isotype.

To determine whether this cross-reactivity was unique to the Ti3a MAb, we analyzed the reactivity of eight different MAbs to Vβ8 gene products, all of which were produced by immunization with the Jurkat T cell line, which expresses a Vβ8.1-encoded TCR β chain variable region (Table IV). All eight anti-Vβ8 MAbs identified similar populations of peripheral blood T cells in two normal individuals. Five of the eight MAbs produced the same cross-reactivity pattern with epithelial cells, suggesting that these MAbs recognized a similar epitope of TCR Vβ8 gene products and that this is a very immunogenic epitope in mice. This epitope is apparently related to an epitope of an as yet unidentified molecule(s) expressed by epithelial cells.

Discussion

A growing number of MAbs to human TCR V region products are being carefully characterized with respect to their specificity for various V gene products (4, 5, 9, 11, 12, 18, 19). These MAbs are useful tools to determine V gene usage by T cells in different tissue sites.

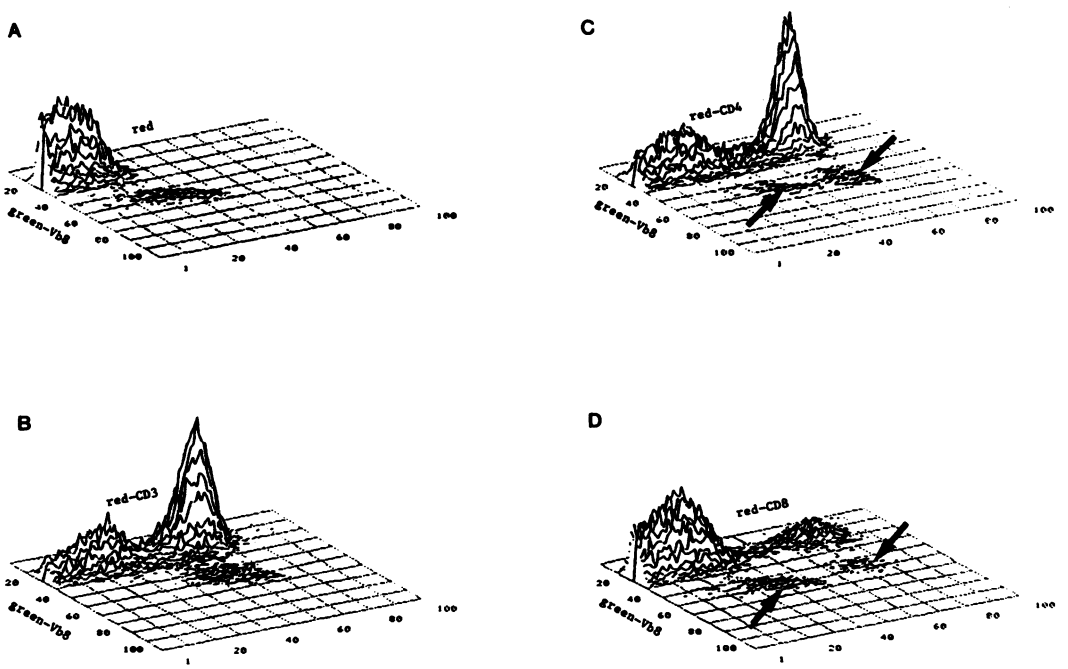

Figure 3. MLN T cells stained with phycoerytherin-conjugated anti-CD3, -CD4, or -CD8 MAb (*red*) and Ti3a (*green*). Ti3a+ cells are all CD3+ (*B*). About 60% of Ti3a+ cells are CD4+ while the rest are CD4− (*C, arrows*). Similarly, 40% of Ti3a+ cells are CD8+ and 60% are CD8− (*D, arrows*).

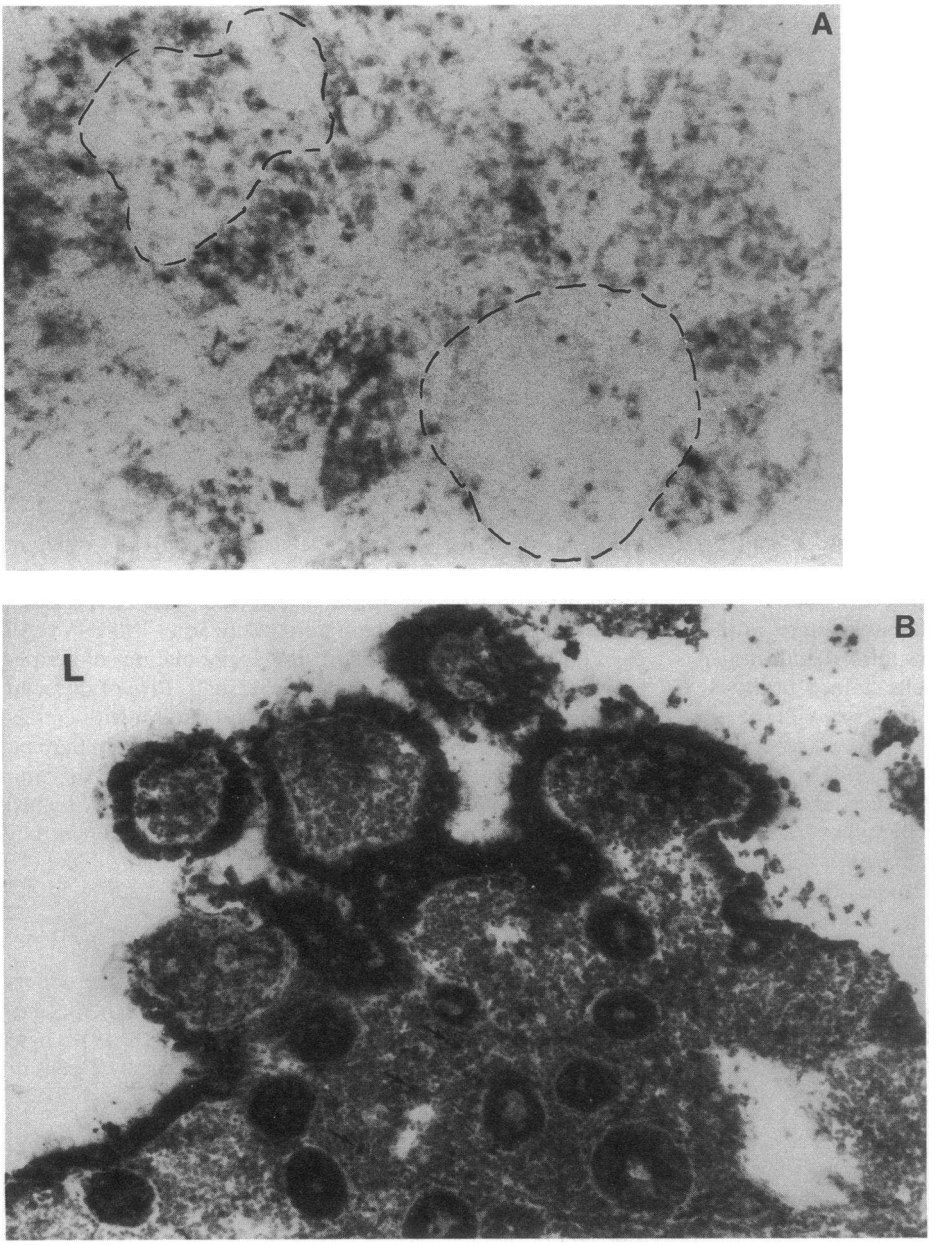

Figure 4. A, Immunoperoxidase staining with Ti3a of a section of MLN from a CD patient stained by immunoperoxidase without counterstain. Location of secondary follicles is outlined. *B,* Immunoperoxidase staining with Ti3a of a section of colonic mucosa from a CD patient with Gill's hematoxylin counterstain. Ti3a+ lymphoid cells within the lamina propria are indicated by arrows. The epithelial cells are strongly positive. *L,* lumen.

Here we report a bias for the usage of Vβ8-encoded gene products in a subset of patients with CD. This bias was not seen in the closely related disease UC, nor in other inflammatory controls, excluding the possibility that the observed Ti3a+ T cells were related to nonspecific inflammation of the bowel.

Since ~ 10% of patients with CD may have family members with either CD or UC (20), a susceptibility gene for both diseases may be inherited in such families. IBD is more prevalent in certain ethnic backgrounds (more common in Jewish individuals), and some groups have reported an increased incidence of CD in individuals with certain immunoglobulin allotypes (21). Monozygotic twins often show concordance for CD (20), and segregation analysis has implicated a recessive susceptibility gene (22). Despite these observations highly suggestive of susceptibility genes for IBD, neither UC nor CD are known to be associated with any HLA types, and patients with CD within the same family are no more likely to share HLA haplotypes than unaffected family members (23, 24). While susceptibility genes for IBD probably exist, they have not yet been identified, and the TCR genes appear to be possible candidates. However, the family studies reported herein did not suggest that the bias towards Vβ8 gene usage was an inherited phenomenon. Other than the proband patients, only two family members (unaffected fathers) with high Ti3a+ T cells were identified, and a pair of identical twins were discordant for Vβ8 expression. Moreover, an RFLP that serves as a marker for the Vβ8.1 gene did not show an association with CD. These data provide no support for the notion that high Vβ8 gene usage in CD is genetically determined or inherited. However, to completely rule out this possibility, further studies of families with IBD will be needed with haplotype assignments of the TCR β chain locus (25).

The Ti3a+ T cells found in excess in some CD patients appear to be concentrated in MLN draining the diseased gut

Table IV. Cross-reactivity of Anti-Vβ8 MAb with Epithelial Cells

MAb	Isotype	Reference	Reactivity with T cells* A	Reactivity with T cells* B	Reactivity with Epithelial cells‡
			%	%	
Ti3a	IgG1	(9)	3.6	4.8	3+
C305.2	IgM	(11)	3.7	6.2	3+
MX11	IgG2	(12)	4.6	5.9	2+
MX9	IgG2	(12)	3.9	5.9	2+
MX12	IgG2	(12)	4.7	6.0	4+
2D1	IgG2a	(TCS)§	4.0	5.0	0–1+
16G8	IgG2b	(TCS)	3.2	6.2	0
12B8	IgG2b	(TCS)	3.7	5.9	0–1+

* Percentage of positive CD3+ T cells in two individuals (*A*) and (*B*) in the peripheral blood.
‡ Immunoperoxidase staining of normal colonic mucosa (0–4 scale for intensity of staining).
§ *TCS*, T Cell Sciences, Inc.

tissues. This finding raised the possibility that screening the peripheral blood–derived T cells may underestimate the actual number of patients with increased Ti3a+ T cells. In fact, > 60% of MLN-derived CD samples demonstrated elevated Vβ8 expression, while only 20% of peripheral blood–derived samples showed elevated Vβ8 expression. The elevated Ti3a+ T cells were found in clusters in T cell–rich interfollicular areas of MLN.

The absence of elevated levels of Ti3a+ T cells in the lamina propria of diseased gut tissues indicates that these cells are primarily involved in the afferent but not the efferent limb of a gut-associated immune response. Moreover, the finding of polyclonal Ti3a+ T cells selectively enriched in CD MLN, the response (in one patient) to surgical removal of diseased tissue, and the absence of an evident genetic factor all suggested that the elevated Ti3a+ T cells were the result of a gut-associated specific immune response. The elevated Ti3a+ T cells would thus represent selective use of a specific Vβ gene product in response to exposure to a specific antigen. Multiple examples of selective Vβ and Vα gene usage have been described among antigen-specific T cells, including the T cell response to cytochrome *c* (26), to a hapten-like trinitrophenyl (27, 28), to the autoantigen myelin basic protein (29, 30), and to superantigens (3, 18).

Therefore, hypothetical causes for the induction of Vβ8+ T cell proliferation in CD might include (*a*) a foreign antigen presented by MHC-encoded molecules, such as an antigen of an enteric bacterium or virus, (*b*) a cross-reactive autoantigen presented on damaged epithelial cells, or (*c*) a foreign or autologous superantigen (3, 18). Recently, a staphylococcal enterotoxin has been found to be a superantigen with specificity for human Vβ8 gene products (18). This antigen or a similar bacterial product could presumably gain access to the immune system via the diseased gut mucosa in CD and selectively induce proliferation of Vβ8+ T cells. An alternative hypothesis, suggested by the cross-reactivity of the anti-Vβ8 MAb with an epithelial cell antigen, would postulate the presence of autoantibodies in CD patients, some of which might cross-react with an epithelial cell antigen and a Vβ8-encoded TCR determinant. Such a putative autoantibody to the TCR would be expected to be mitogenic (5, 31) for Vβ8+ T cells. Some preliminary data have been generated in favor of such a possibility (32), based on studies with sera from two patients. Further studies on this question are in progress.

The bias for Vβ8 gene usage but not Vβ12, 5, or 6, in CD is comparable to recent findings in sarcoidosis (33, 34; our unpublished data). Both CD and sarcoidosis are chronic granulomatous diseases of unknown origin with certain pathologic similarities. It may be no coincidence that the same Vβ8 genes are involved in both of these diseases, particularly in light of the absence of any bias observed in peripheral blood T cells with other Vβ gene families in several other diseases (5).

Acknowledgments

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