The Vδ1 T Cell Receptor Repertoire in Human Small Intestine and Colon

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Summary

Vδ1 bearing T cells comprise the major population of γ/δ T cells in the human intestinal tract. To gain insight into mechanisms involved in the generation of these cells and the diversity of their repertoire, we have characterized the junctional sequences of Vδ1 T cell receptor transcripts in the human small intestine and colon. Mucosal biopsies obtained from defined regions along the length of the small intestine or colon contained a high frequency of either one or a few identical in frame Vδ1 sequences. Less abundant sequences were also detected repeatedly throughout the length of small intestine or colon. Moreover, the intestinal Vδ1 repertoire in the small intestine and colon appeared compartmentalized and showed no overlap with the Vδ1 repertoire in peripheral blood. Dominant Vδ1 transcripts in each subject differed between the small intestine and colon, and the dominant transcripts within these sites differed among individuals. Analysis of small intestinal transcripts obtained at a 1-yr interval revealed that the Vδ1 repertoire was stable over time. The fact that the majority of Vδ1 transcripts, both dominant and rare, are distributed throughout a several meter length of the adult intestinal tract and are stable over time suggests they are not generated by an ongoing process of in situ VDJ gene rearrangement. Our results favor a model in which the repertoire of Vδ1 T cells in the intestinal tract is shaped by positive selection in response to a limited array of ligands before the migration of Vδ1 cells throughout the small intestine or colon.
are highly limited in the repertoire of ligands they recognize and that V81 cells in adult human small intestine and colon are not generated by an ongoing process of in situ TCR rearrangement.

Materials and Methods

Intestinal Biopsies and PBMC. Colonic biopsies, 2–3 cm apart, were obtained from normal appearing mucosa of three healthy unrelated adult males undergoing screening flexible sigmoidoscopy. Biopsies were also obtained from the sigmoid colon, splenic flexure, transverse colon, and hepatic flexure of a fourth individual (OJ) with a normal colonoscopic exam. Small intestinal biopsies were obtained from the third portion of the duodenum in five individuals with a normal upper intestinal endoscopy. Both colon and small intestinal biopsies were obtained from three of the subjects (FA, PJ, and PL) and, in one subject (KE), biopsies were obtained from the small intestine at two different time points, 1 yr apart. Mucosal biopsies from the colon and small intestine were 2–3 mm in size. Since mucosal biopsies include both the surface epithelial layer and lamina propria, TCR-β transcripts may derive from γ/δ T cells in either of these compartments. PBMCs, obtained at the time of intestinal biopsy, were separated from whole blood by Ficoll-Hypaque density gradient centrifugation, and stored frozen until use. All experiments were approved by the UCSD Committee on Human Subjects.

RNA Extraction, Reverse Transcription, and V81-specific PCR Amplification. RNA was extracted from biopsies and PBMCs using an acid–phenol extraction method (14). 1 μg total cellular RNA was reverse transcribed in 20 μl using 100 ng oligo(dT)12 primer (Boehringer Mannheim Corp., Indianapolis, IN) and murine Moloney leukemia virus reverse transcriptase (Superscript; Gibco BRL, Gaithersburg, MD), under conditions recommended by the manufacturer. Negative controls from which RNA was omitted were included in each experiment.

After first strand cDNA synthesis, PCR amplification was performed using either primer set I or primer set II. Primer set I consists of V81 5’AAAGTCGACGTAACAAACCTTCACGCAAAGG’ and C8 5’GCATGCCGGCCGCTCTTATCTCTTGAGATCGACGAC’ and generates products of ~400 bp. Primer set II consists of V81 5’ATAAGTCGACGTAACAAACCTTCACGCAAAGG’ and C8 5’TTGATGATGCGGCCGCTCTTATCTCTTGAGATCGACGAC’ and generates products of ~650 bp. Primer set II is complementary to sites located upstream and downstream of the region defined by primer set I. Each primer contained Sall or NotI restriction site extensions (underlined) to facilitate directional cloning into pBlue-script II SK+ (Stratagene), La Jolla, CA).

PCR products included 1–2 μl of the reverse transcription reaction, 2.5 U Taq DNA polymerase (Stratagene), 0.2 mM of each dNTP (Pharmacia P-L Biochemicals, Inc., Milwaukee, WI), and 1 μM primers in 100 μl buffer supplied by the manufacturer. After an initial hot start, amplification cycles consisted of 1 min denaturation at 95°C, 1 min annealing at 54°C, and 1 min extension at 72°C, followed by a final extension period of 10 min at 72°C after 35 cycles. Each reverse transcription reaction was amplified in triplicate. In addition, each experiment included negative controls from the reverse transcription reaction, and negative controls in which the PCR reagents, but no cDNA, were included. Strict procedures were followed to prevent cross contamination in reverse transcription and PCR reactions (15). PCR products were analyzed by electrophoresis in 1% agarose gels.

To determine whether V81 transcripts found in the intestine are also present in PBMCs, amplifications were performed using the V81 primer from set II in combination with a primer complementary to junctional sequences of dominant clones SI.FA02 (5’CCGATATATGGTGTTCC), C.FA01 (5’GGGACCCTGTAFCCTAATC) or C.PJ22 (5’CCGAGTGGAAAGACOGGC) under conditions identical to those described above. Amplification products were analyzed in 2% agarose gels.

Cloning and Sequencing of PCR Products. Pooled amplification products from three reactions were purified using QiAquick-spin PCR columns (Qiagen Inc., Chatsworth, CA), digested with 30 U of Sall and NotI and cloned into pBlue-script SK+ (Stratagene). Recombinant plasmid DNA from color-selected colonies was purified and sequenced by the dideoxy chain termination method using Sequase (United States Biochemical Corp., Cleveland, OH) and the C8 primer 5’ACCGATGTGTGGCTATGG3’.

Nucleotide sequences were assigned to TCR-β gene segments based on at least 3 bp identities to published J (16) and D (17) germline sequences.

Reverse Transcription and PCR Amplification Control. To assess the possibility of preferential reverse transcription and/or PCR amplification of selected V81 transcripts, plasmid DNA carrying dominant or rare sequences were transcribed using T7 RNA polymerase (Stratagene). RNA was purified and separated from DNA by acid phenol extraction (14). 10 ng sense RNA were mixed with 200 ng total mouse thymus RNA and reverse transcribed using T3 primer (Stratagene). After reverse transcription, serial 10-fold dilutions ranging from 10 to 0.01 pg of single stranded cDNA product from the rare and dominant clones were amplified as described above. Amplification products were size fractionated in ethidium bromide stained 1% agarose gels, photographed using 665 film from Polaroid Corp. (Cambridge, MA), and the negative image was quantitated by densitometry (Image Densitometer, model GS-560; Bio-Rad Laboratories, Richmond, CA). Comparisons were made in a concentration range where the yield of product proportionally reflected the starting amount of cDNA.

Results

V81 Transcripts in the Small Intestine. Fig. 1 shows the V81 junctional sequences and the frequency of each sequence in small intestinal biopsy specimens from three individuals. In subjects KE and TP, a single dominant sequence was detected, although a broader population of sequences was also present. PL displayed a more diverse repertoire. For each subject, V81 transcripts were derived from a pool of three biopsies that were obtained 2–3 cm apart. To verify that the increased frequency of certain intestinal TCR-β transcripts accurately reflected an increased prevalence of these transcripts in the biopsy mRNA, and not a technical bias due to preferential reverse transcription and/or PCR amplification of selected transcripts, identical amounts of sense RNA generated using plasmids carrying four dominant and four rare sequences were reverse transcribed and PCR amplified as described in Materials and Methods. The yield of amplification products from the rare and dominant sequences was similar supporting the lack of substantial sequence based bias of our methods (data not shown).

The finding of dominant V81 transcripts in pooled biopsies of two subjects suggested that the repertoire of V81 bearing γ/δ T cells in the small intestine was restricted. If this were the case, individual biopsies from a limited region of small
intestine would contain identical dominant Vβ1 transcripts. To address this possibility, two separate small intestinal biopsies were obtained 2-3 cm apart from two additional subjects (FA and PJ). As shown in Fig. 2, within each subject, each biopsy contained the same dominant transcripts.

We next asked whether, within an individual, the same Vβ1 transcripts were also dominant in distant parts of the small intestine and if the pattern of expressed transcripts was stable over time. For these experiments, 1 yr after the first analysis was performed, a second set of biopsies from the third...
Table 1. The Repertoire of Vδ1 Transcripts Is Similar in the Duodenum and Ileum and Remains Constant Over Time

| Site of biopsy | Date of biopsy | Clone SI.KE09 | Clone SI.KE24 | Clone SI.KE30 | Clone SI.KE31 | Clone SI.KE32 | Clone SI.KE07 | Total no. of clones sequenced |
|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|-----------------------------|
| Duodenum‡     | 8/92          | 3             | 2             | 0             | 0             | 1             | 1             | 19                          |
| Duodenum‡     | 9/93          | 5             | 4             | 1             | 2             | 1             | 1             | 19                          |
| Terminal ileum| 9/93          | 6             | 4             | 2             | 0             | 0             | 0             | 14                          |

* Sequence data for these cDNA clones are available from EMBL/GenBank/DBJ under accession numbers L32374, L32375.
† Biopsies were obtained from the third portion of the duodenum.
§ Numbers refer to the number of cDNA clones carrying a specific Vδ1 junctional sequence. All transcripts were in frame except SI.KE07.

A portion of the duodenum and the terminal ileum was obtained from subject KE. To prevent any possible contamination from products of our previous analysis, experiments were carried out using primers complementary to sites external to the prior amplification products (primer set II). As shown in Table 1, the repertoire of Vδ1 transcripts in the duodenum was similar over a 1-yr time span, with clone SI.KE09 being the most prevalent. Moreover, a similar repertoire of dominant and rare Vδ1 sequences was present in both the duodenum and terminal ileum which are approximately 4–7 m apart.

Vδ1 Transcripts in the Colon. Junctional sequences of TCR Vδ1 transcripts from the colon are shown in Fig. 3. In the small intestine, a few sequences predominated in each biopsy, although other sequences were also present at a low frequency. Also like the small intestine, identical dominant transcripts were present in different colonic biopsies obtained ~2–3 cm apart. Dominant transcripts in the colon differed from those in the small intestine of the same individual and between subjects. However, as shown in Fig. 3, five transcripts present in the colon were also detected, at a low frequency, in the small intestine (indicated by prefix SI).

We next asked whether, like the small intestine, a limited number of dominant transcripts was present throughout the colon. For this experiment, biopsies were obtained from the sigmoid colon, splenic flexure, transverse colon, and hepatic flexure of a fourth subject. As shown in Table 2, a

Figure 3. Vδ1 junctional sequences from individual colonic biopsies. Vδ1 transcripts were cloned and sequenced as described in Materials and Methods. In subjects FA and PJ, two separate biopsies were obtained at a distance of 2–3 cm apart (I and II), whereas in subject PL a single biopsy was obtained. Numbers indicate the number of DNA clones having each junctional sequence. Primers and complementary genomic sequences are indicated in bold print and underlined. Sequences in and out of frame are indicated by (+) or (−), respectively. As shown, clone C.PA1I predominated in biopsy I and II from subject FA, whereas clone C.PJ22 was dominant in biopsy I and II from subject PJ. Clone C.PLI2 was dominant in subject PL. These sequence data are available from EMBL/GenBank/DBJ under accession numbers L32444, L32481.
similar pattern of dominant and rare Vδ1 sequences was found throughout the length of the colon. Finally, we note that only four junctional sequences (i.e., SI.PA02, SIKE09, C.PJ20, and C.FA36) were shared between any two subjects (Figs. 2 and 3).

Vδ1 Transcripts in Peripheral Blood. To test the possibility that the dominant Vδ1 transcripts in the intestine also are present in peripheral blood, Vδ1 transcripts were cloned and sequenced from PBMCs obtained at the same time as the intestinal biopsies. As shown in Fig. 4, the peripheral blood also contained dominant Vδ1 sequences. However, none of the dominant or rare Vδ1 transcripts present in peripheral blood overlapped with those in the intestine. Moreover, dominant Vδ1 transcripts present in the small intestine and colon were not detected in PBMC when reverse transcribed cDNA from PBMC was PCR amplified with primers specific for the junctions of dominant intestinal Vδ1 transcripts and a Vδ1-specific primer (Fig. 5). This was also the case when samples from the first PCR reaction were reamplified under the same conditions (data not shown).

Molecular Features of Vδ1 Transcripts. 63/73 (86%) Vδ1 junctional sequences from the small intestine and 61/70 (87%) sequences from the colon were in frame. Moreover, junctional regions were highly complex. J segment usage contributed little to the junctional diversity, since the majority of the sequences used J61 (i.e., the J82 segment was used in only one
and the Jβ3 segment was used in only five sequences from small intestinal biopsies (Figs. 1 and 2). Dδ3 and Dδ8 segments were used most frequently and often in combination (i.e., Dδ3 was present in 93% of small intestinal transcripts and 87% of colonic transcripts; Dδ8 was present in 81% of small intestinal transcripts and 73% of colonic transcripts). Nucleotide sequences that could be assigned to the Dδ3 segment were used most frequently and often in combination (i.e., Dr was present in 93% of small intestinal transcripts and 73% of colonic transcripts).

**Discussion**

These studies demonstrate a highly restricted repertoire of Vδ1 bearing γ/δ T cells in the human small intestine and colon. Sequence-specific primers in patient PJ amplified with primers specific for the junction of transcript CFA01. Lanes 1–3 represent cDNA amplified with primers specific for the junction of transcript SLFA02. Lane 1, cDNA from colon; Lanes 2 and 5, cDNA from PBMC; Lane 4, cDNA from small intestine; Lanes 3 and 6, No cDNA control. Not shown, similar results were obtained in parallel studies using a sequence-specific primer in patient PJ.

**Figure 5.** Vδ1 transcripts present in the intestine are not found in PBMC. cDNA from PBMC and intestinal biopsies that were obtained concurrently from subject FA was amplified with junction specific oligonucleotides as described in Materials and Methods. Lanes 1–3 represent cDNA amplified with primers specific for the junction of transcript FA01. Lanes 4–6 represent cDNA amplified with primers specific for the junction of transcript SLFA02. Lane 1, cDNA from colon; Lanes 2 and 5, cDNA from PBMC; Lane 4, cDNA from small intestine; Lanes 3 and 6, No cDNA control. Not shown, similar results were obtained in parallel studies using a sequence-specific primer in patient PJ.

**Figure 6.** Predicted junctional amino acid sequences encoded by Vδ1 transcripts from the small intestine and colon. The three possible reading frames for each Dδ segment are shown. Numbers refer to the number of cDNA clones having each junctional sequence within the small intestine and colon of each subject. The single letter code used for amino acids is that recommended by the IUPAC (26).
colon. Thus, in each individual, mucosal biopsies from throughout the length of the small intestine or colon expressed one or a few dominant in frame Vδ1 transcripts. In addition, rare sequences were used repetitively throughout the small intestine or the colon. The dominant transcripts in each subject differed between the small intestine and colon and the dominant transcripts in these sites differed among subjects. Moreover, as tested in one subject, our analysis revealed that the Vδ1 repertoire in the small intestine was stable over a 1-yr period. The intestinal Vδ1 repertoire showed no overlap with the Vδ1 repertoire in peripheral blood.

The finding of in frame dominant Vδ1 transcripts in the small intestine and colon favors a model wherein the repertoire of Vδ1 bearing γ/δ T cells in the intestine is influenced by positive selection and clonal expansion in response to a limited number of ligands. In mice, the presence of dominant clones of γ/δ T cells has been demonstrated in the skin, vagina, and tongue (3-5), and it was suggested that programmed TCR-γ/δ gene rearrangement in the thymus accounts for the generation of these populations (19, 20). The junctional sequences associated with such populations contain unmodified germline encoded elements with minimal insertions of N nucleotides (3-5, 19, 20). In contrast, the significant complexity of the Vδ1 junctional sequences reported herein indicates that positive selection, rather than programmed rearrangement, plays a major role in shaping of the repertoire of Vδ1 cells located in the human gut. Moreover, the restricted repertoire of transcripts present throughout the entire length of the small intestine or colon, coupled with stability of the repertoire over time, indicates that the repertoire of Vδ1 T cells in the intestinal tract is selected before the migration of these cells throughout the intestine. Although the exact site of Vδ1 gene rearrangement could not be determined, these data do not support a model in which the dominant clones are generated by a process of continuous in situ Vδ1 TCR gene rearrangement, in which case a more diverse and changing δ T cell repertoire would be expected.

The CDR3 domains of the TCR δ chains have the potential for extensive molecular diversity which suggests that γ/δ T cells can recognize a broad array of ligands (1). This does not appear to be the case for Vδ1 cells. The finding that Vδ1 transcripts in both the small intestine and colon are markedly oligoclonal suggests the repertoire of ligands recognized by these cells in the intestine is highly restricted. This finding is even more striking given the diverse bacterial flora present in the colon. Further, the stability of the Vδ1 repertoire over a 1-yr period suggests that in healthy individuals, the array of ligands recognized by these cells is also relatively stable over time and is not markedly affected by possible variations in the endogenous microbial flora and dietary antigens. This is consistent with studies showing that the intestinal flora, as assessed in germ-free and specific pathogen-free mice, has a marked effect on the representation of α/β but not γ/δ T cells (21).

The differences in the repertoire of dominant Vδ1 transcripts in the small intestine compared to the colon and peripheral blood suggest differences in the spectrum of ligands recognized by the Vδ1 cells in those sites. As in the intestine, predominant Vδ1 transcripts were detected in the PBMC population, a finding in agreement with others (22). However, Vδ1 transcripts in the small intestine and colon differed from those in peripheral blood. Thus, dominant Vδ1 transcripts found in the intestine were not detected in peripheral blood either by direct cloning or by junction specific PCR analysis. Taken together, these data support the notion that Vδ1 T cells are compartmentalized.

In contrast to γ/δ IELs, human α/β IELs in the small intestine and colon are reported to use multiple Vβ gene segments (23, 24). However, V segment usage between individuals differed quite markedly (23) and analysis of Vβ junctional sequences within individuals demonstrated marked oligoclonality (23-25). Since those studies used pooled IEL from intestinal segments rather than the sampling of defined regions, it is not known whether the extent of TCR β chain oligoclonality in the small intestine and colon parallels that noted herein for Vδ1.

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