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Effects of HIV-1 Peptides on T-Cell Receptor Variable β Chain Families

Angelia Eick, Josh Larned, and Janine Jason

ABSTRACT: Superantigens (SAGs) selectively stimulate expansion and then deletion of specific T cell antigen receptor (TCR) variable beta chain (Vβ) families. We investigated six synthetically produced HIV-1-related peptides for evidence of SAG activity: three derived all or in part from the transmembrane gp41 protein and three from the genetic sequence of the tRNA binding region. The first three were chosen because they are highly immunogenic; the second three, because their genetic sequence is completely homologous to a region of the mouse mammary tumor virus, a known superantigen. We cultured peripheral blood mononuclear cells (PBMC) of HIV-negative, healthy human donors with each of these six HIV-1 peptides. Resting and blastic $CD4^+$ and $CD8^+$ lymphocytes were assessed pre- and post-culture using 3-color cytofluorometry and monoclonal antibodies to CD4, CD8, and 14 human TCR Vβ families. Significance testing was done using a Student *t*-test. Two of the HIV-1 peptides showed possible SAG activity, one from gp41 transmembrane protein, and one from tRNA binding region. Peptide JJ1, from gp41, was associated with an increased percentage of resting and blastic Vβ 5, 8, and 21 in $CD4^+$, but not $CD8^+$ lymphocytes (3/3 donors, $p = 0.014$, $p = 0.011$, and $p = 0.019$, respectively, for blastic $CD4^+$ lymphocytes). Peptide JJ5, from the tRNA binding region, was associated with an increased percentage of resting and blastic Vβ 5, 12, 16, and 17 in $CD8^+$ but not $CD4^+$ lymphocytes (4/4 donors for blastic $CD8^+$ lymphocytes, 3/4 for resting $CD8^+$ lymphocytes, $p < 0.05$ for each Vβ family, for blastic $CD8^+$ lymphocytes). These results suggest that peptide JJ1 may have SAG activity restricted to $CD4^+$ lymphocytes and that peptide JJ5 may have restricted cytotoxic activity, associated with $CD8^+$ cell responsiveness. For both, the activities would lead to increased localized cytokine production and work to the advantage of the virus. These antigens might thus represent potential targets for future antiretroviral therapy. *Human Immunology 61, 993–1000 (2000).* © American Society for Histocompatibility and Immunogenetics, 2000. Published by Elsevier Science Inc.

KEYWORDS: HIV; superantigens; TCR

INTRODUCTION

Superantigens (SAGs) typically cause the specific expansion and then deletion of certain T cell antigen receptor (TCR) variable beta chain (Vβ) families; specific SAGs each stimulate their own particular pattern of Vβ families. Several known SAGs include those expressed endogenously in inbred mice, genetically encoded by murine retroviruses, and exogenous bacteria, including the enterotoxins of *staphylococci* and *streptococci* [1]. SAGs bind to the Vβ of the TCR, outside of the antigen-binding cleft [1, 2]. They are known to stimulate and delete T cells with specific TCR Vβ chain families, leading to either amplification or suppression of immune responses [1]. Because human immunodeficiency virus (HIV) interacts with, infects, and then finally causes extensive destruction of $CD4^+$ lymphocytes activity and also causes expansion, and eventual destruction of $CD8^+$ lymphocytes, it has been suggested that HIV might have antigens with SAG activity [3–8].

A previous study from our laboratory examined potential SAG activity of HIV antigens on the TCR Vβ. We found some Vβ-specific, statistically significant $CD4^+$ lymphocyte decreases and $CD8^+$ lymphocyte expansions; however, the effects were slight and we questioned their physiological significance [9]. Other studies have reported Vβ-specific effects with HIV infection but conflict with one another in terms of the Vβ families involved and stage of HIV at which the effects were seen [7, 8, 10–12].

To further investigate the possibility of Vβ stimulation by HIV, we studied the *in vitro* effects of each of six

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TABLE 1 HIV-1 related peptides investigated for potential superantigen activity

Peptide name	Amino acid sequence	Region
JJ1	RILAVERYLKDQQLLGIWGCSGKLIC	gp41[a]
JJ2	AVGIGALFLGFL	gp41
JJ3	AVGIGALFLGFLKQIINMWQEVGKAMYA	gp41/gp120[b]
JJ4	APLVSLSLSSPCSGATARDFPH	tRNA
JJ5	ELLWFPFRFQVPVRAPLLEIFHTD	tRNA
JJ6	FSQCGKSLAVAPEQGLESERETRGAL	tRNA

[a]gp41 aa 584-609 [15]; [b]a construct of the fusogenic domain of HIV gp41 and the T helper epitope of HIV gp120 [14].

HIV-1 related peptides (Table 1) on the TCR Vβ family distributions of resting and blastic $CD4^+$ and $CD8^+$ peripheral blood lymphocytes (PBL) of HIV-negative, healthy human donors. These peptides were synthetically synthesized [13]. Three were derived from the transmembrane protein gp41, one of which was a peptide constructed from the fusogenic domain of HIV gp41 and the T helper epitope of gp120 [14, 15]. These were chosen because they are known to be highly immunogenic. Three other peptides were derived from a portion of the tRNA binding region of HIV and were chosen because there is complete homology between their genetic sequence and that of a region of the open reading frame (ORF) in the leading terminal repeat (LTR) of a mouse mammary tumor virus (MMTV), associated with known SAG activity (Genbank accession number S68403). Staphylococcal enterotoxin D (SED) was used as a positive control antigen, because it has well-defined SAG activity.

MATERIALS AND METHODS

Cells and HIV Reagents

The following six HIV-1-specific peptides were obtained (Protein Chemistry Section, Biological Core Facility, CDC, Atlanta, GA, USA) in lyophilized form: JJ1 through JJ6 (Table 1). Peptides JJ1–JJ3 were derived from the gp41 and gp120 regions of HIV. Peptide JJ6 was derived from a portion of the tRNA binding region of HIV, while peptides JJ4 and JJ5 were obtained by frame shifts in peptide JJ6. The peptides were synthesized by Fmoc chemistry on an ACT Model 350 multiple peptide synthesizer (Advanced ChemTech, Louisville, KY, USA) according to the manufacturer's protocols [13]. The peptides were characterized by amino acid analysis, high performance liquid chromatography, and capillary electrophoresis. SED (Serva Biochemicals, Westbury, NY, USA) was dissolved in PBS prior to addition to culture media.

Venous blood was obtained from seven healthy donors prescreened and negative for antibodies to hepatitis A, B, and C viruses, human T-cell lymphotrophic viruses (HTLVs), and HIV. Blood was drawn into heparinized vacutainers and peripheral blood mononuclear cells (PBMCs) were isolated from these samples. Analysis of PBMCs was performed both before and after culture. Culture media was prepared with RPMI-1640 containing 2 mM L-glutamine, 10% fetal bovine serum, and the cell culture was split into five different aliquots. Each cell aliquot was placed into culture with one peptide (0.1 μg/ml) or SED (0.001 μg/ml). A SED "positive control" was done for each experiment (data not shown). Peptides JJ1–JJ3 were examined in PBMCs of three donors and JJ4–JJ6, in PBMCs of four donors. PBMCs were maintained in culture at 2×10^6 cells/ml for 4 to 7 days at 37°C, 5% CO_2. Cell aliquots were placed into culture with each peptide once per donor and one full panel of Vβ distributions was obtained per donor. We have previously shown that without these peptides, SAGs, or stimulation other than with PHA, the Vβ distribution of PBMCs does not change under these culture conditions [9, 16]. The survival under these culture conditions ranges from 25%–50%.

Other Reagents

Fluorescein isothiocyanate-conjugated (FITC) monoclonal antibodies against the human TCR Vβ families were acquired from the following sources, with reactivities specified to date as follows: Immunotech (Westbrook, ME, USA; Vβ 2.1, clone E22E7.2; Vβ 3.1, clone LE-89; Vβ 5.2, clone 36213; Vβ 8.1/.2, clone 56C5.2; Vβ 11.1, clone C21; Vβ 13.6, clone JU74.3; Vβ 14.1, clone CAS1.1.3; Vβ 16.1, clone TAMAYA1.2; Vβ 17.1, clone E17.5F3.15.13; Vβ 20.1, clone ELL1.4; Vβ 21.3, clone IG.125; Vβ 22.1, clone IMMU 546), T Cell Diagnostics (now Endogen, Woburn, MA, USA; Vβ 3.1, clone 8F10 (designated "3A" by the manufacturer); Vβ 5.1, clone LC4; Vβ 5.2/.3, clone 1C1; Vβ 5.3, clone W112; Vβ 6.7, clone OT145; Vβ 8, clone MX-6 (designated "8B" by the manufacturer); Vβ 12, clone S5111; Vβ 13.1/.3, clone BAM13), Becton Dickinson (Mountain View, CA, USA; TCR-α/β, clone WT31; anti-CD3). Phycoerythrin-conjugated (PE) monoclonal anti-CD8 and PerCP-conjugated (PerCP) monoclonal anti-CD4 were obtained from Becton Dickinson.

Flow Cytoflurometry

Three-color cytoflurometry was performed using a FAC Sort (Becton Dickinson) and Lysis II software or Cell Quest software (Becton Dickinson), as described previously [9, 16]. The flow cytometer was calibrated daily using Becton Dickinson calibration beads for FITC, PE, and PerCP. Isotype controls were stained with FITC mouse IgG1, PE mouse IgG2a, and PerCP mouse IgG1.

In general, 20,000 to 30,000 ungated events were collected from each sample and an additional 3000 events were collected from each sample using the following gating: (a) forward and side-scattering of TCRα,β^+ cells indicative of large (blastic) cells, as opposed to small (resting) lymphocytes; and (b) positivity for CD4 or CD8, but not both. Previous research shows that this scatter gate is below the monocytes and forward of most cell clumps and doublets (data not shown) [9, 16]. Also, a 27-gauge syringe was used to break up any clumping. In addition, gating on single populations positive for CD4 or CD8 was done, which would eliminate clumps or doublets including both cell types. Three thousand blastic T lymphocytes were evaluated in each analysis [9, 16]. Analyses were performed on the following populations: resting $CD4^+$ lymphocytes, resting $CD8^+$ lymphocytes, blastic $CD4^+$ lymphocytes, and blastic $CD8^+$ lymphocytes.

Analytical and Statistical Techniques

After subtraction of isotype control values, comparisons were made between percentages of resting and blastic $CD4^+$ and $CD8^+$ lymphocytes expressing a given Vβ chain family at the end of culture and resting and blastic $CD4^+$ and $CD8^+$ lymphocytes expressing a given Vβ chain family at the onset of culture. Readings at both time points are performed on the same machine, with the same compensation, and by the same operator. All analyses were conducted with consistent gating between time points.

Percentages of $CD4^+$ or $CD8^+$ lymphocytes expressing TCR Vβ "X" at the end of culture were compared with percentages of lymphocytes expressing Vβ "X" at the beginning of culture (day 0) by means of a paired Student *t*-test. In order to preserve matching of individual cultures (post- to preculture), data herein will be expressed as the mean subtractive differences between the proportion of cells expressing that Vβ at the end of culture and the proportion of resting $CD4^+$ and $CD8^+$ lymphocytes expressing that Vβ on day 0, for all cultures done with that antigen.

The significance level for all analyses was set at 0.05. In addition, we will provide information on the proportion of experiments for which a specific directionality of change was found, *e.g.*, an increase was seen with three out of four donors, $p = 0.010$.

RESULTS

Peptide JJ1 was associated with an increased percentage of $CD4^+$ resting ("R") (Figure 1A) and, especially, blastic ('Bl') (Figure 1B) lymphocytes expressing Vβ 5.3, 8, and 21.3 at the end of culture, compared with the *ex vivo* value (Vβ 5.3: $\overline{\times}$: D0 0.8%, R 1.0%, Bl 1.5%; $p = 0.014$ for Bl) (Vβ 8: $\overline{\times}$: D0 3.0%, R 3.8%, Bl 5.2%; $p = 0.011$ for Bl) (Vβ 21.3: $\overline{\times}$: D0 1.7%, R 2.2%, Bl 2.6%; $p = 0.023$ for R and $p = 0.019$ for Bl). These increases were seen in 3 of 3 donors. No significant changes in percentages were seen in $CD8^+$ lymphocytes (data not shown).

Peptide JJ3 was associated with statistically significant shifts in Vβ family distributions; however, the Vβ families and directions of change varied by donor and by cell type involved. In three of three donors, Vβ 22 percentages increased in resting $CD8^+$ lymphocytes (Figure 2A) and blastic $CD4^+$ (Figure 2B) lymphocytes ($CD8^+$ $\overline{\times}$: D0 2.3%, R 3.1%, $p = 0.007$; $CD4^+$ $\overline{\times}$: D0 3.6%, Bl 4.7%, $p = 0.03$). However, for resting $CD4^+$ and blastic $CD8^+$ lymphocytes, Vβ 22 percentages varied in the direction of change and thus the changes were not statistically significant. Changes in Vβ 12 and Vβ 13.1/.3 were significant only for blastic $CD4^+$ lymphocytes. Because of the variability in findings associated with JJ3, we cannot make inferences about SAG activity and this peptide.

Peptide JJ5 was associated with an increased percentage of resting (Figure 3A) and blastic $CD8^+$ (Figure 3B) lymphocytes expressing a wide variety of Vβ families. Changes for two families were present in both resting and blastic cells, consistent in direction for all donors, and statistically significant: Vβ 5.3 (D0 0.8%, R 1.5%, Bl 1.7%, $p = 0.027$ for R; 4 of 4 donors) and Vβ 12 (D0 0.3%, R 0.8%, Bl 1.4%, 0.027 for R; 4 of 4 donors). Increased percentages of blastic $CD8^+$ lymphocytes expressing Vβ 5.2/.3 (D0 1.8%, Bl 5.6%, $p = 0.002$; 4 of 4 donors), Vβ 16 (D0 0.5%, Bl 2.0%, $p = 0.015$; 4 of 4 donors) and Vβ 17 (D0 1.7%, Bl 4.1%, $p = 0.017$; 4 of 4 donors) were also associated with peptide JJ5.

No statistically significant expansions or deletions were seen with JJ2, JJ4, and JJ6 (data not shown).

DISCUSSION

We examined whether six synthetically derived HIV-associated peptides possessed SAG activity, based on their ability to stimulate expansion or diminution of specific TCR Vβ families in HIV-uninfected PBMCs. The six peptides included three amino acid sequences derived from the transmembrane gp41 protein and three amino acid sequences derived from a genetic sequence in the tRNA binding region of HIV genetically homologous to the MMTV SAG [14, 15]. Previous studies have investigated the possibility of HIV SAG activity [3–12]. These studies examined the expansion/deletion of Vβ families due to HIV infection or HIV antigens. However, none of these studies have looked specifically at two regions of the HIV genome that could well be associated with SAG activity. The gp41 region related to JJ1–3 is

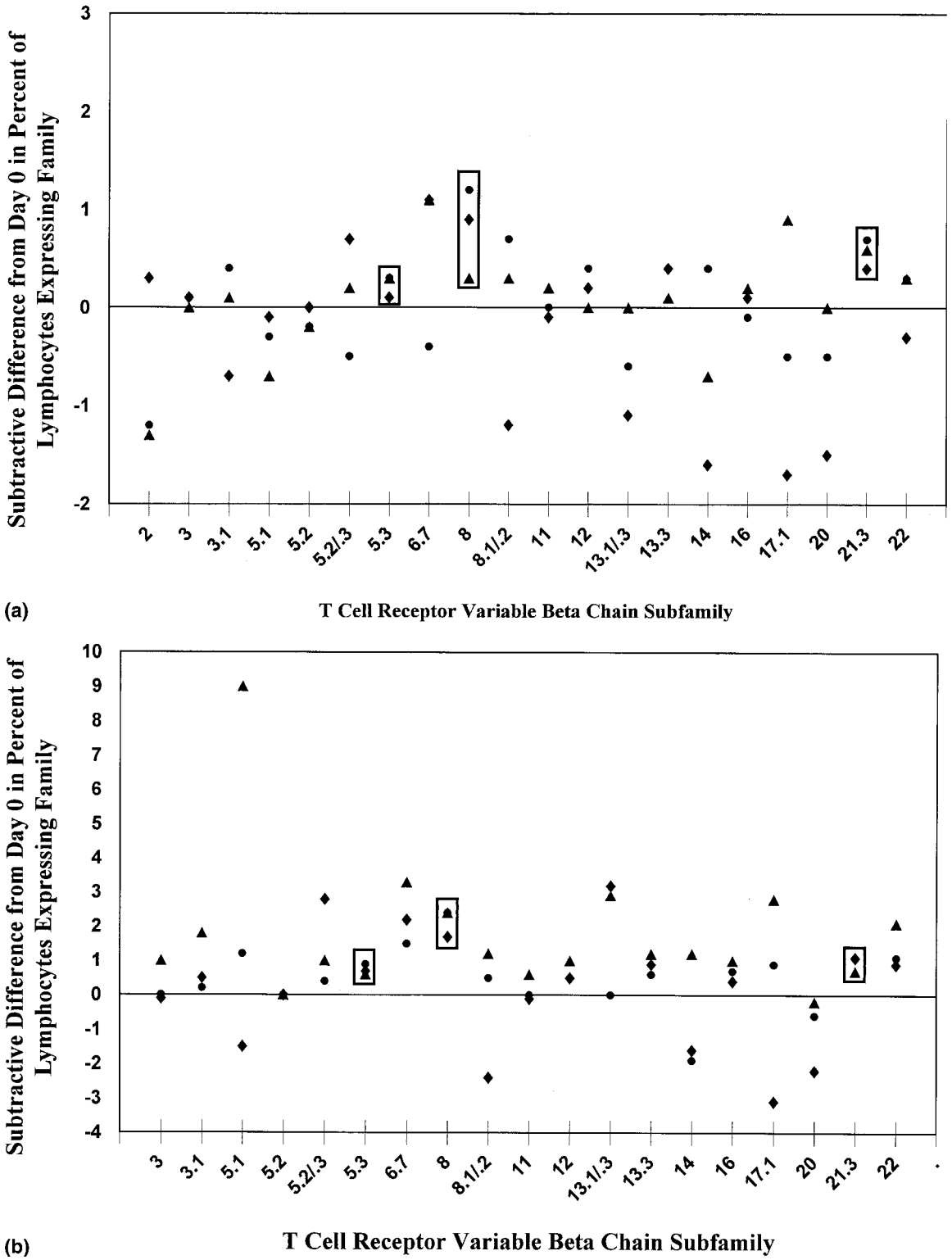

FIGURE 1 (A) Changes in resting $CD4^+$ lymphocytes expressing various TCR Vβ subfamily gene products, associated with peptide JJ1. Each symbol represents a different donor and symbols are consistent between Figures 1A, 1B, 2A, and 2B. Boxed symbols represent significant results. Resting lymphocytes were determined using forward and side scatter gating as described in the text. (B) Changes in blastic $CD4^+$ lymphocytes expressing various TCR Vβ subfamily gene products, associated with peptide JJ1. Each symbol represents a different donor and symbols are consistent between Figures 1A, 1B, 2A, and 2B. Boxed symbols represent significant results. Blastic lymphocytes were determined using forward and side scatter gating as described in the text.

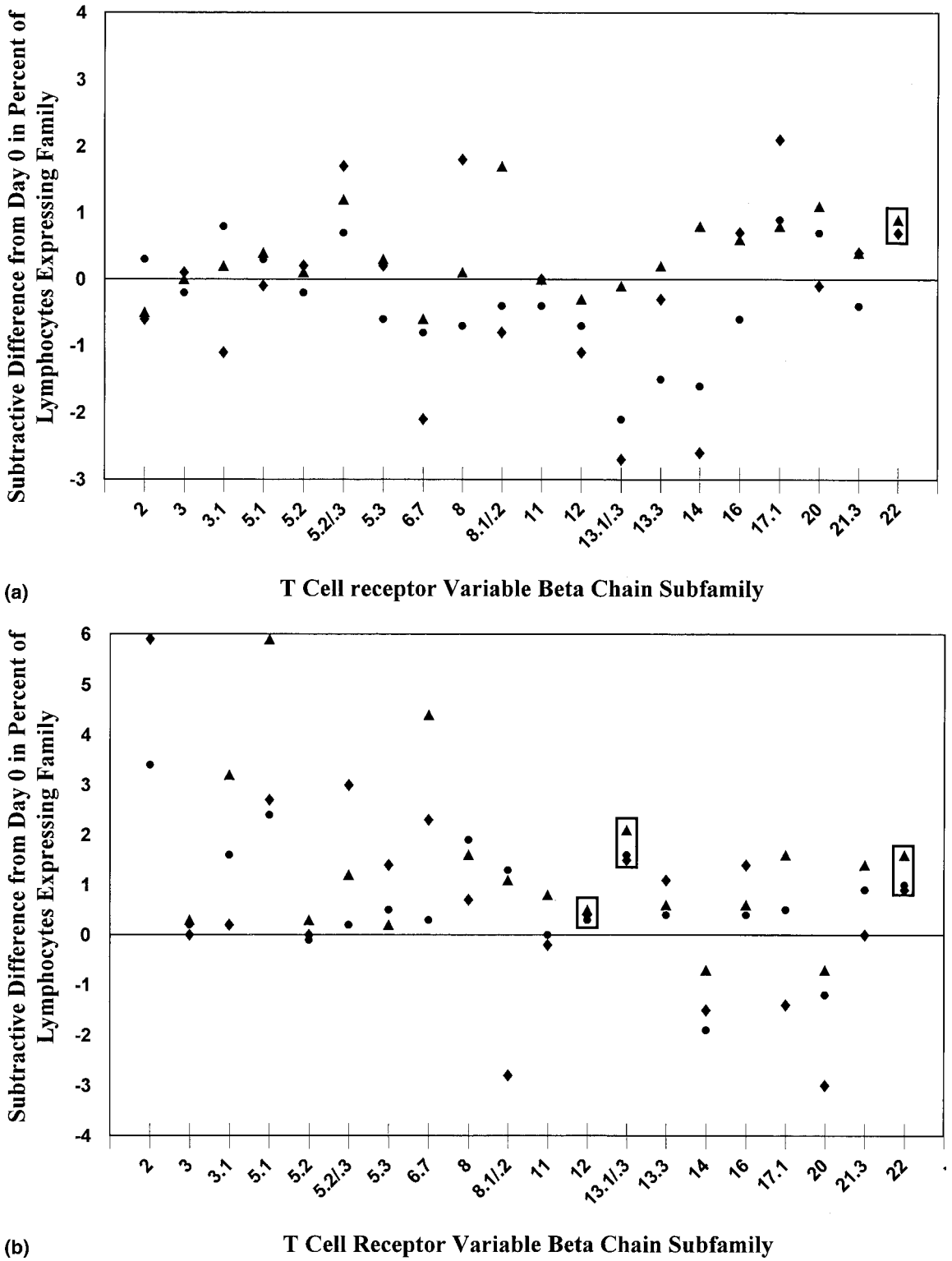

FIGURE 2 (A) Changes in resting $CD8^+$ lymphocytes expressing various TCR Vβ subfamily gene products, associated with peptide JJ3. Boxed symbols represent significant results. Resting lymphocytes were determined using forward and side scatter gating as described in the text. (B) Changes in blastic $CD4^+$ lymphocytes expressing various TCR Vβ subfamily gene products, associated with peptide JJ3. Each symbol represents a different donor and symbols are consistent between Figures 1A, 1B, 2A, and 2B. Boxed symbols represent significant results. Blastic lymphocytes were determined using forward and side scatter gating as described in the text.

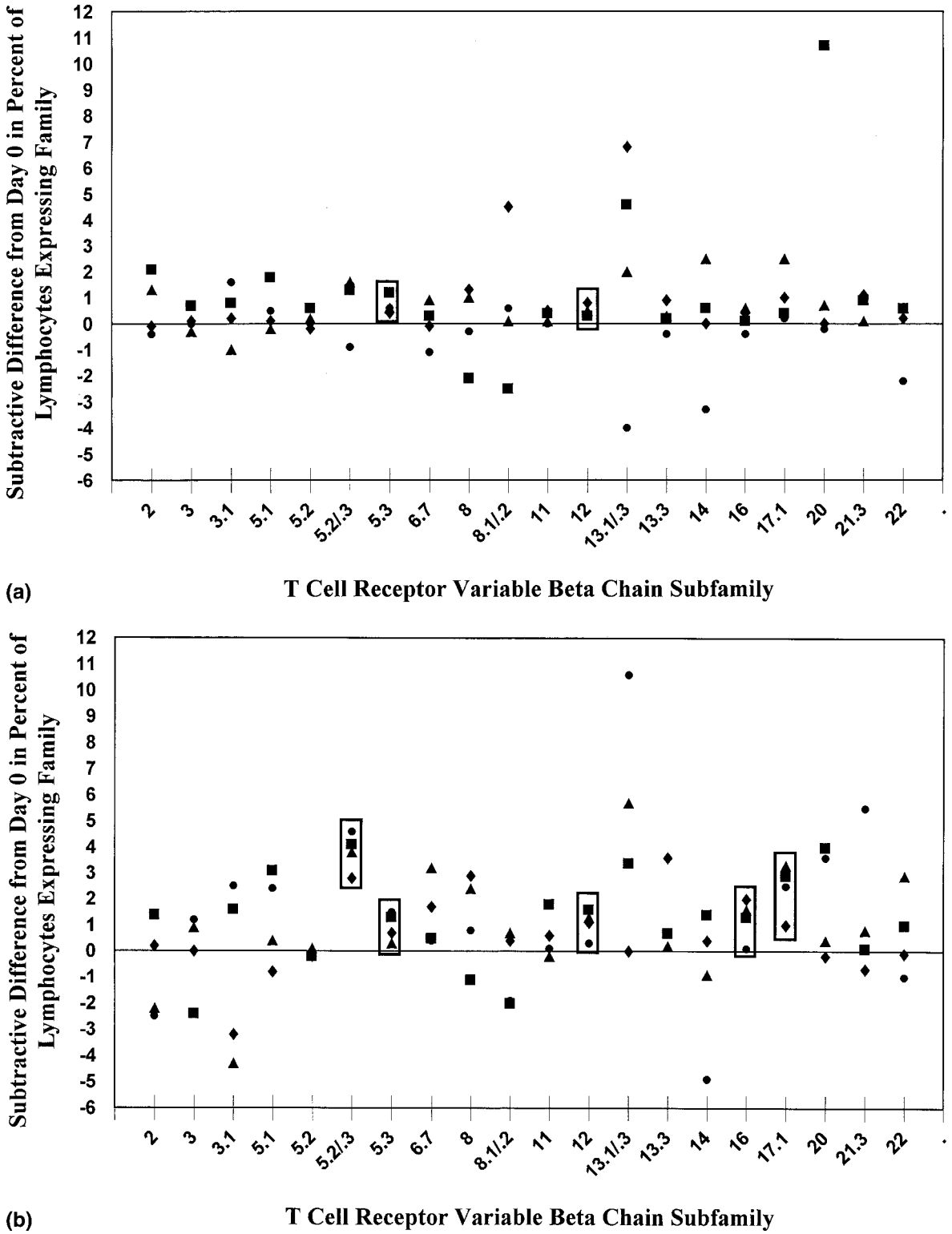

FIGURE 3 (A) Changes in resting $CD8^+$ lymphocytes expressing various TCR Vβ subfamily gene products, associated with peptide JJ5. Each symbol represents a different donor and symbols are consistent between Figures 3A and 3B. Boxed symbols represent significant results. Resting lymphocytes were determined using forward and side scatter gating as described in the text. (B) Changes in blastic $CD8^+$ lymphocytes expressing various TCR Vβ subfamily gene products, associated with peptide JJ5. Each symbol represents a different donor and symbols are consistent between Figures 3A and 3B. Boxed symbols represent significant results. Blastic lymphocytes were determined using forward and side scatter gating as described in the text.

highly immunogenic and a highly related peptide (gp41 aa 584–604) spontaneously associates *in vitro* with diverse class I and II HLA molecules [15, 17]. The portion of the tRNA binding region related to JJ4–JJ6 shares complete sequence homology with a region of the ORF in the LTR of a MMTV having known SAG activity and the ability to interact with both mouse and human MHC class II [14, 15, 18] (Genbank accession number S68403). We examined the ability of the peptide sequences associated with these regions to expand or diminish specific TCR Vβ families, since this is evidence for SAG activity.

Our results support that peptide JJ1, a gp41 peptide, may possess SAG activity selective for $CD4^+$ lymphocytes. Expansions or deletions of Vβ-specific $CD4^+$ lymphocytes has previously been reported with retroviral-encoded SAGs and HIV infection [8, 19–24]; the Vβ families expanded by JJ1 (Vβ 5, 8, 21) are those reported by some investigators to be expanded by HIV infection [21]. Various reasons for $CD4^+$ restriction of SAG activity have been cited [8, 9]; because SAG activity requires MHC class II binding and CD4 binds MHC class II [25], there may be differentially greater stability of SAG binding in $CD4^+$ lymphocytes. Further JJ1, itself may bind CD4, further stabilizing the binding. SAG activity would help explain the relatively great immunogenicity of gp41, in terms of increased numbers of $CD4^+$ helper cells and increased cytokine production within the microenvironment of gp41-bound cells. TCR binding by gp41 would also assist in cell-to-cell transmission of HIV, not by viral entry at the TCR but rather by localized production of cytokines, including interleukin-2 (IL-2), which is known to induce viral replication.

Peptide JJ5, derived from the tRNA binding region of HIV, might also possess SAG activity. However, unlike peptide JJ1, peptide JJ5 stimulated the expansion of TCR Vβ families in $CD8^+$ lymphocytes. Vβ-restricted, $CD8^+$ lymphocyte-specific effects have been reported for a number of pathogens, including Toxoplasma gondii, influenza A, herpes simplex virus, HTLV-I, HIV, and MMTV [26–33]. Thus, the effect of JJ5 may reflect a restricted cytotoxic T lymphocyte responsiveness to the antigen, rather than SAG activity. $CD8^+$ lymphocyte Vβ restriction has been described in both acute and ongoing clinical HIV infection [32, 34]. If JJ5 is in fact a peptide produced by HIV, its $CD8^+$ lymphocyte-restricted activity might be related to these clinical findings and may play a role in HIV's pathogenesis. However, a restricted Vβ repertoire could severely limit the host's ability to respond adequately to the virus. Indeed, in the report showing Vβ-restricted HIV antigen-related cytotoxic activity, that activity was extremely weak [32]. In a study of MMTV, Mls-1^a-specific $CD8^+$ T cells produced IFN-γ but could not lyse Mls-1^a-bearing target cells [33].

In summary, we found evidence for potential SAG activity with one HIV gp41-related polypeptide and potential restricted cytotoxic T-cell responses to one synthetically produced polypeptide related to the MMTV genetic sequence. The activity of the first polypeptide was $CD4^+$ lymphocyte-restricted; the activity of the second was restricted to $CD8^+$ lymphocytes. For both, their activities would be to the advantage of the virus. These antigens might thus represent potential targets for future antiretroviral therapy.

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