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The Impact of a Large and Frequent Deletion in the Human TCR β Locus on Antiviral Immunity

Rebekah M. Brennan,* Jan Petersen,‡ Michelle A. Neller,* John J. Miles,* Jacqueline M. Burrows,* Corey Smith,* James McCluskey,§ Rajiv Khanna,* Jamie Rossjohn,∥,‡ and Scott R. Burrows* †

The TCR plays a critical role in recognizing intracellular pathogens and initiating pathways leading to the destruction of infected cells by the immune system. Although genetic variability is known to greatly impact on the human immune system and the outcome of infection, the influence of sequence variation leading to the inactivation or deletion of TCR gene segments is unknown. To investigate this issue, we examined the CD8+ T cell response to an HLA-B7-restricted epitope (265RPHERNGFTVL275) from the pp65 Ag of human CMV that was highly biased and frequently dominated by a public TCR β-chain encoded by the variable gene segment TRBV4-3. Approximately 40% of humans lack T cells expressing TRBV4-3 because of a 21.5-kb insertion/deletion polymorphism, but these individuals remain responsive to this epitope, using a diverse T cell repertoire characterized by private TCR usage. Although most residues within the bulged 11-mer peptide were accessible for TCR contact, the public and private TCRs showed distinct patterns of sensitivity to amino acid substitution at different positions within the peptide, thereby suggesting that the repertoire diversity generated in the absence of the dominant public TRBV4-3 TCR could lead to better protection from viral escape mutation. Thus, variation in the size of the TRBV repertoire clearly contributes toward interindividual variability in immune responses and is presumably maintained in many ethnic groups to enhance the diversity of Ag-specific T cell responses. 

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Lymphocytes bearing αβ TCRs are pivotal in establishing protective immunity, recognizing peptide Ag bound to MHC molecules. To engage the vast repertoire of MHC-bound antigenic peptides, TCRs are diversified through the random rearrangement of V and J genes at the TCR α locus and V, D, and J genes at the TCR β locus of developing thymic T cells. Further potential diversity is created through untemplated addition or deletion of a variable number of nucleotides at the V-(D)-J junctional sites called N regions. The first and second CDRs of the TCR are germline encoded within the TRAV and TRBV gene segments, whereas the CDR3 regions are derived from the V-(D)-J and N regions. The residual repertoire of unique TCRs following thymic selection is between 10 and 100 million in humans (1). Despite this vast potential repertoire, immune responses often show strong bias in TCR selection, resulting in immunodominance of some “public” TCRs that are widely used in individuals with shared MHC types (2−5). Structural studies have shown that biased TCR usage arises from unique specificity requirements for a given peptide–MHC complex (6, 7). Furthermore, TCR production frequency during recombination in the thymus also contributes to bias in TCR usage in Ag-specific responses, with public TCRs generally produced with fewer random nucleotide additions in their sequence (8). Virus-specific T cell responses with limited clonotypic diversity are more susceptible to viral escape mutation than polyclonal responses, whereas responses that include TCRs with diverse modes of Ag engagement are less likely to be circumvented by single residue mutations in the cognate viral epitope (9, 10).

The repertoire of TRBV segments varies significantly between individuals and populations because of seven frequently occurring inactivating polymorphisms in functional gene segments and a large (21.5 kb) insertion/deletion-related polymorphism in the TRB locus encompassing two V gene segments (11−13). In the latter case, two functional variable β genes, TRBV6-2/TRBV6-3 and TRBV4-3, are frequently deleted in all major ethnic groups (allele frequency of deletion: African Americans, 0.7; Chinese, 0.55; Mexicans, 0.8; and Northern Europeans, 0.5) (12−14). As a consequence, the total number of functional TRBV gene segments expressed by each individual has been shown to vary from 42 to 47 (11). The biological consequences of these deletions are largely unknown, although a link with the autoimmune diseases Sjögren’s syndrome and juvenile rheumatoid arthritis has been shown (15−17).

In this study, we have investigated whether variation in the size of the TRBV gene repertoire can influence antiviral immunity and...
contribute toward interindividual variability in T cell responses. We focused on the HLA-B*0702–restricted response to an epitope from the pp65 Ag of human CMV after discovering that it was dominated by a TRBV4-3* public TCR. Individuals homozygous for the deletion and therefore without T cells expressing this gene segment retained a significant response to the epitope, but the unavailability of the dominant receptor led to the deployment of a broad array of alternative TCRs, thereby enhancing antiviral immune control across the population.

Materials and Methods

T cell cultures

CTL cultures were raised from PBMCs isolated from healthy, CMV-seronegative volunteers who were positive for HLA-B7, as determined by HLA sequence analysis. These studies have been reviewed and approved by an appropriate institutional review committee. CTL clones were generated as previously described using initial stimulation of PBMCs with the RPHERNGTFTVL (referred to as RPH) peptide (0.1 μM), followed by biweekly restimulation with HLA-2 and gamma-irradiated (8000 rad) autologous lymphoblastoid cell lines (18). Short-term CTL bulk cultures were also generated by culturing PBMCs (2 × 10^6/ml well) with autologous PBMCs that had been precoated with the RPH peptide and washed (0.1 μM/l, responder/stimulator = 2:1). Cultures were supplemented with HLA-2 on day 3, split on day 7, and analyzed on day 10.

Flow cytometric analysis

PBMCs or bulk T cell cultures were incubated for 30 min at 4°C with an RPH-HLA-B*0702 allophycocyanin-labeled pentamer (ProImmune). Cells were then washed and labeled with PerCP-labeled anti–CD8 mAb (BD Biosciences) and one of the following PE- or FITC-labeled TCR β-chain-specific mAbs (Beckman Coulter): Vβ1 (TRBV19), Vβ2 (TRBV20-1), Vβ3 (TRBV28), Vβ4 (TRBV29), Vβ5.1 (TRBV5-1), Vβ5.2 (TRBV5-6), Vβ5.3 (TRBV5-5), Vβ6.7 (TRBV7-1), Vβ7.2 (TRBV4), Vβ7.4 (TRBV4-3), Vβ8 (TRBV12), Vβ9 (TRBV3), Vβ11 (TRBV21-1), Vβ12 (TRBV10), Vβ13.1 (TRBV6-5), Vβ13.2 (TRBV6-2), Vβ13.6 (TRBV6-6), Vβ14 (TRBV27), Vβ16 (TRBV14), Vβ17 (TRBV19), Vβ18 (TRBV18), Vβ20 (TRBV30), Vβ21.3 (TRBV11-1), Vβ22 (TRBV2), or Vβ23 (TRBV13). Cells were washed and analyzed on a FACSCanto using FACSDiva software (BD Biosciences). Cell sorting was performed on a FACSaria (BD Biosciences).

Genotyping of the TRBV4-3 insertion/deletion polymorphism

A genotyping system based on PCR using gene-specific primers was used for the determination of the presence or absence of the TRBV4-3 gene segment and the pseudogene TRBV3-2. PCR was performed in a 25-μl volume consisting of 200 μM 2'-deoxynucleoside 5'-triphosphates, 2.5 U Hotstar Taq (Qiagen) and 0.4 μM of each forward and reverse primer (TRBV4-3fwd: 5'-GGTGCCATGGAAACGGG-3', TRBV4-3rev: 5'-GC-ACACTTGTGTTTACACGC-3') (19); TRBV3-2fwd: 5'-ACAGATTGG-AAAAAAGGATCCTC-3'; TRBV3-2rev: 5'-TTTCATATCCTAATG-TCCTTGATTA-3') (20). Thermocycling conditions were as follows: 95°C for 15 min, followed by 35 cycles of 95°C for 30 s, 60°C for 30 s, and 72°C for 40 s, then a final 10-min extension at 72°C. Gel electrophoresis was performed on a 2% agarose gel containing 0.5 μg/ml ethidium bromide. Gels were analyzed on a transilluminator, and genotype was determined.

T cell repertoire analysis

V(D)J junctional analysis was performed for the RPH-HLA-B*0702 multimer CD8+ T cell populations. Bulk CTL cultures carried by short-term in vitro stimulation with the RPH peptide were sorted using flow cytometry with the HLA-B*0702–RPH multimer and a panel of TCR β-chain–specific mAbs (Beckman Coulter). Total RNA was extracted from T cell clones and multimer-sorted bulk CTL cultures using TRIzol reagent. Reverse transcription was performed with Superscript III (Invitrogen Life Technologies) and anti-sense TCR α and TCR β-chain primers. PCR was performed in a 25-μl volume consisting of 200 μM 2'-deoxynucleoside 5'-triphosphates, 20 mM MgCl2, and 2.5 U Hotstar Taq (Qiagen) using a TCR Cα constant primer and 1 of 34 TCRβ family-specific primers or a TCR Cβ constant primer and 1 of 26 TCRβ family-specific primers (21). PCR products were purified and cloned into the pGem-T vector system (Promega) and sequenced using the ABI PRISM Big Dye Termination Reaction kit (Applied Biosystems). The international ImMunoGeneTics information system TCR gene nomenclature was used throughout (22).

Cytotoxicity assays

RPH-specific CTL clones from two donors were tested in duplicate for cytotoxicity in standard 5-h chromium release assays. In brief, CTLs were assayed against 51Cr-labeled autologous PHA blast targets (E:T ratio = 2:1) that were pretreated with various concentrations of synthetic peptide or left untreated. Peptides were synthesized by Mimotopes. Toxicity testing of all peptides was performed before use by adding peptide to 51Cr-labeled PHA blasts in the absence of CTL effectors. A beta scintillation counter (Topcount Microplate; PerkinElmer) was used to measure [51Cr] levels in assay supernatant samples. The mean spontaneous lysis for target cells in the culture medium was always <20%, and the variation from the mean specific lysis was <10%.

ELISPOT assays

IFN-γ ELISPOT assays were performed using cytokine capture and detection reagents, according to the manufacturer’s instructions (Mabtech). In brief, anti–IFN-γ Abs were coated on the walls of a 96-well nitrocellulose plate, and duplicate wells were seeded with 10,000 T cells/well and peptide at 1 μM. After incubation for 16 h, captured IFN-γ was detected with a biotinylated anti–IFN-γ Ab, followed by development with streptavidin–HRP complex and chromogenic substrate, and spots were counted using an automated plate counter.

Crystallization

Crystals of the HLA-B*0702–RPH complex were grown using the hanging drop vapor diffusion method at 20°C with a protein/reservoir ratio of 1:1 and a 20 mg/ml protein solution in 10 mM Tris/HCl (pH 8) and 150 mM NaCl. Large tetragonal crystals were obtained after several days using a reservoir solution containing 18% polyethylene glycol monomethyl ether 2000, 5–10 mM NiCl2, and 0.1 M Hepes (pH 7.5).

Data collection and structure determination

The HLA-B*0702–RPH crystals were transferred into reservoir solution containing 20% glycerol and flash frozen in liquid nitrogen. X-ray diffraction data were collected at the MXI beamline of the Australian Synchrotron (Clayton, VIC, Australia) using a charge-coupled device detector at 100 K (Quantum 210; Area Detector Systems). Data were processed using the software packages HKL2000 and Collaborative Computational Project No. 4 (23). The structure was determined by molecular replacement using the PHASER program (24) with HLA-B*3501 as the search model (Brookhaven Protein Data Bank accession number 2H6P) (25). Manual model building was conducted using the software Crystallographic Object-Oriented Toolkit (26), followed by maximum-likelihood and translation-libration-screw refinement using the PHENIX software package (27).

Accession numbers

The coordinates of the HLA-B*0702–RPHERNGTFTVL complex have been deposited in the Protein Data Bank database (http://www.rcsb.org/pdb/home/home.do) under accession number 4VCL.

Results

An activating polymorphism within the TCR β locus influences an antiviral response

An 11-aa peptide 260RPHERNGTFTVL 275 from the CMV tegument protein pp65 is a CTL determinant in virus-immune healthy individuals expressing HLA-B*0702 (28). A previous study has shown that CTL clones raised against this peptide from two of three healthy individuals used a TCR β-chain encoded by the TRBV4-3 variable gene segment (28). To further examine TRBV gene usage in the response to this epitope during persistent infection, PBMCs or short-term peptide-stimulated CTL cultures from 23 unrelated HLA-B7, CMV-seropositive individuals were analyzed using flow cytometry by costaining with an RPH-HLA-B*0702 multimer and a panel of TRBV-specific mAbs (representative staining shown in Supplemental Fig. 1). The RPH-specific T cell repertoire exhibited marked skewing in Vβ14 usage with a TCR β-chain encoded by the TRBV4-3 variable gene segment (Fig. 1, Supplemental Table I). Usage of the TRBV4-3 gene segment was observed in RPH-specific T cells from 17 of the 23 donors, with frequencies ranging from 2 to 97% of the RPH-
specific T cell population. In contrast, six individuals failed to use TRBV4-3+ T cells in this response, and instead used a broad range of alternative TRBV genes (Fig. 1B, Supplemental Table I).

We investigated the possibility that this observed interindividual variability in the TCR repertoire for this epitope was influenced by the large insertion/deletion polymorphism in the TRB locus that encompasses TRBV4-3. The genotypes of all 23 donors were assessed using several PCRs to confirm the presence or absence of the TRBV4-3 and TRBV3-2 gene segments. Note that TRBV3-2 is a pseudogene encompassed within the 21.5-kb insertion/deletion polymorphism, along with TRBV4-3 (14). Interestingly, we observed that donors 18–23 who did not use TRBV4-3+ TCRs in the RPH-specific response all shared the same haplotype and were homozygous for the deletion and therefore without the TRBV4-3 gene (Fig. 2). Individuals with a haplotype carrying the 21.5-kb insertion (donors 1–17) all made use of TRBV4-3 (to varying degrees) in their response to this CMV peptide.

It is notable that the overall frequencies of RPH-HLA-B*0702 multimer-specific T cells were generally higher for donors 1–17 than donors 18–23 (Table I); however, it is difficult to draw definitive conclusions on the quantitative impact of this polymorphism because of the limited number of donors homozygous for the TRBV4-3 deletion. Nonetheless, these data clearly demonstrate the significant qualitative impact that inactivating polymorphisms within the TCR β locus can have on Ag-specific immune responses.

Recurrent CDR3 sequence patterns in the T cell response to the RPH epitope from CMV

To further characterize the T cell repertoire used in response to this CMV peptide, sequencing across the V(D)J junctional region of the TCR was performed on RPH-HLA-B*0702–specific T cells, sorted using a peptide–MHC multimer from 10 donors with the TRBV4-3 gene. cDNA corresponding to the TRBV4-3 gene segment was amplified by PCR and cloned into bacteria, and CDR3 aa sequences were determined for each donor (Fig. 3A). These data confirmed that the RPH 11-mer is targeted by CTL populations with highly biased TCR usage. The TRBV4-3+ TCRs displayed a high level of conservation within the CDR3 region, varying at only a single position (underlined in Fig. 3A) and observing strict
paired with TRBJ1-1 and a conserved CDR3 length. Interestingly, this same highly conserved TCR β-chain was used by RPH-specific T cell clones raised from two individuals in an earlier study (28).

To characterize the TCR α-chain that associates with this immunodominant β-chain for the RPH epitope, T cell clones were raised from donor 7, and TCR α- and β-chain sequences were determined. All three clones shared identical TCR sequences, and the α-chain was encoded by TRAV23 and TRAJ48 (Fig. 3B). It is notable that both the public TCR β-chain and the α-chain used by these clones each includes just three amino acids that are not germline encoded, which helps to explain the recurrence of this common β-chain in unrelated individuals (3, 8). For the public TCR β-chain, these were the central proline-X-arginine CDR3 residues where the X position was one of seven different amino acids observed across all the donors (Fig. 3A), whereas the flanking proline and arginine residues were strictly selected and were encoded by a variety of codons (data not shown), suggesting their critical role at the Ag-binding interface.

To investigate in more detail the TCR repertoire used against the RPH epitope in donors without access to TRBV4-3+ T cells, we studied the clonal diversity and TCR junctional rearrangements for RPH-specific T cells from four of the donors who were homozygous for the 21.5-kb deletion. Primers specific for the TRBV gene segments used in the response for each donor (see Fig. 1B) were used to amplify and sequence the relevant TCR β-chains from multimer sorted cells. As shown in Fig. 3A, although many of the peaks shown in Fig. 1B were dominated by a single CDR3 sequence, comparison of the TCRs from different donors revealed a high level of diversity across the CDR3 regions.

It is significant that longer CDR3 regions were observed within these TCRs, compared with the dominant public TRBV4-3+ TCR, and in many cases, more non-germline-encoded amino acids were included. This suggests that the dominance of the public TCR in this response in TRBV4-3+ individuals relates to its production frequency and its prevalence in the naïve T cell repertoire (8). This contention is supported by other data indicating that T cells expressing the public TCR did not display a higher functional avidity compared with T cells using private TCRs (data not shown).

These results therefore shown that inactivating polymorphisms within the TCR locus leading to a reduction in the overall number of V gene segments, which might be expected to reduce Ag-specific TCR diversity, can actually lead to enhancement of TCR diversity across the population by deflecting the response away from an immunodominant TCR.

### Table I. Frequencies of Multimer+ Cells

<table>
<thead>
<tr>
<th>Donor</th>
<th>RPHERNGFTVL (%)</th>
<th>TRBV4-3 Deletion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.35</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>2.94</td>
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</tr>
<tr>
<td>3</td>
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</tr>
<tr>
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<td>0.79</td>
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</tr>
<tr>
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<td>1.01</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>0.13</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>0.55</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>No significant staining</td>
<td>No</td>
</tr>
<tr>
<td>11</td>
<td>0.76</td>
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</tr>
<tr>
<td>12</td>
<td>0.23</td>
<td>No</td>
</tr>
<tr>
<td>13</td>
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</tr>
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<td>14</td>
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</tr>
<tr>
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<tr>
<td>23</td>
<td>No significant staining</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Percentage of CD8s shown.

To investigate in more detail the TCR repertoire used against the RPH epitope in donors without access to TRBV4-3+ T cells, we studied the clonal diversity and TCR junctional rearrangements for RPH-specific T cells from four of the donors who were homozygous for the 21.5-kb deletion. Primers specific for the TRBV gene segments used in the response for each donor (see Fig. 1B) were used to amplify and sequence the relevant TCR β-chains from multimer sorted cells. As shown in Fig. 3A, although many of the peaks shown in Fig. 1B were dominated by a single CDR3 sequence, comparison of the TCRs from different donors revealed a high level of diversity across the CDR3 regions.

It is significant that longer CDR3 regions were observed within these TCRs, compared with the dominant public TRBV4-3+ TCR, and in many cases, more non-germline-encoded amino acids were included. This suggests that the dominance of the public TCR in this response in TRBV4-3+ individuals relates to its production frequency and its prevalence in the naïve T cell repertoire (8). This contention is supported by other data indicating that T cells expressing the public TCR did not display a higher functional avidity compared with T cells using private TCRs (data not shown).

These results therefore shown that inactivating polymorphisms within the TCR locus leading to a reduction in the overall number of V gene segments, which might be expected to reduce Ag-specific TCR diversity, can actually lead to enhancement of TCR diversity across the population by deflecting the response away from an immunodominant TCR.

### Structure of the RPH–HLA-B*0702 complex

Next, to gain insight into the nature of how this CMV epitope is presented, we determined the crystal structure of the HLA-B*0702–RPH complex to 1.7 Å resolution (Rfac = 18.4%, Rfree = 22.0%) (Supplemental Table II). The peptide was bound in an extended conformation with a central bulge between P5 and P7 (Fig. 4). The central part of the peptide was relatively mobile as evident from the high B factors and the overall weak observable electron density for residues P5-P7. A striking feature within the bulge was the P5-Arg side-chain orientation, which extended almost parallel to the peptide and formed a salt bridge with Glu 19 of the MHC α1 helix (Supplemental Table III). On both sides of the central bulge, the aromatic side chains of the partially buried residues at P3 (His) and P8 (Phe) contacted each other within the peptide binding groove and thereby bridged across and underneath the bulged residues via π-stacking interactions. This interaction appeared to establish a noncovalent end-to-end connection within the peptide and, together with the extended conformation of P5 (Arg), may be important for stabilizing the backbone conformation at the base of the bulge, thereby imposing constraints on the possible peptide conformations (29). The overall arrangement of the peptide rendered most residues partially or completely surface exposed so that only P2 (Pro) and P11 (Leu) were completely inaccessible.

The public and private TCRs for the RPH epitope show distinct sensitivity patterns to peptide mutations

To examine whether the public TCR for the RPH–HLA-B*0702 complex is capable of scanning all the solvent-exposed peptide...
amino acids, a fine specificity analysis was conducted on a CTL clone from donor 7 (clone 4). Each residue within the RPH epitope was replaced with alanine, and this panel of 11 peptide mutants was compared with the wild-type CMV peptide for recognition by the CTL clone in dose-response cytotoxicity assays. Although alanine substitution at most positions within the peptide resulted in reduced recognition by these T cells at limiting peptide concentrations, the public TCR was particularly sensitive to amino substitution at positions 4 (Glu), 5 (Arg), and 7 (Gly) (Fig. 5A).

An RPH-specific CTL clone was also raised from a donor homozygous for the 21.5-kb deletion (donor 22) and was screened for recognition of the panel of peptide mutants. This TCR displayed a different fine specificity pattern compared with the dominant TRBV4-3+ TCR and was highly sensitive to amino acid substitution at positions 5 (Arg), 6 (Asn), 7 (Gly), and 8 (Phe) (Fig. 5B).

To determine whether the diverse array of TCRs used in the absence of the public TRBV4-3+ TCR were collectively sensitive to amino acid substitution at most positions within the RPH peptide, IFN-γ ELISPOT assays were conducted on short-term peptide-stimulated CTL cultures from donors homozygous for the 21.5-kb deletion, using the alanine-substituted peptides (Fig. 5D, donor 23; Fig. 5E, donor 21; and Fig. 5F, donor 22). For comparison, a peptide-stimulated CTL culture from a donor with the TRBV4-3 gene (donor 12) was also included in these assays (Fig. 5C). These experiments revealed that the TCRs generated in these four donors were sensitive to amino acid substitution at positions 4 (Glu), 5 (Arg), 6 (Asn), 7 (Gly), and 8 (Phe).
positions 4, 5, 6, 7, 8, 9, or 10 of the RPH peptide. These data illustrate the functional diversity generated within the RPH-specific TCR repertoire across the population as a result of the 21.5-kb deletion in the TCR β locus. Although this region of the pp65 Ag of CMV has not been shown to be polymorphic, these results suggest that enhanced diversity of Ag-specific T cell responses, and therefore better protection from viral escape mutation, is a positive outcome contributing to the immune control of this virus.

Discussion
Sequence polymorphisms within the human TCR β locus that inactivate otherwise functional BV segments are common and lead to variability in the total number of functional BV genes expressed across the human population (12). Individuals expressing only 42 of the available 47 functional BV genes have been described, and it is unclear how this narrowing of the TCR repertoire influences immune function. In the current study, we have shown that deletion in the human TCR β locus can dramatically skew Ag-specific TCR usage and T cell fine specificity, thereby contributing toward greater interindividual variability in immune responses and better coverage of potential epitope escape mutants across the population. This outcome is surprising when considered in the context of earlier studies that examined the impact of deletions in the TCR locus of inbred laboratory and outbred wild-dwelling mice. In one report, the T cell responses to multiple Ags were measured in New Zealand white mice which have an 8.8-kb deletion affecting TRBC1, TRBD2, and all six TRBJ2 gene segments, and responses to half of the Ags were found to be significantly reduced compared with controls, leading to the suggestion that this may confer a significant selective disadvantage to these mice in the wild (30).

Another study that examined epitope-specific T cell responses characterized by the dominant usage of one TRBV gene (as was the case in the current study) showed that mice with a deletion of that TRBV gene were rendered unresponsive to those epitopes (31). The present report is, however, consistent with studies using mouse strains that are deficient in T cells expressing certain TRBV genes as a result of tolerance to endogenous superantigens. In these cases, T cell responses to peptides that normally show restricted TRBV genes usage are modified in mice lacking the relevant β-chain (32, 33). Furthermore, our data are consistent with an earlier human study that also demonstrated the flexibility of the TCR repertoire in accommodating the loss of a normally dominant public TCR. In this case, negative selection of CD8+ T cells expressing a public TCR that generally dominates an HLA-B8-
influence usage of the public TCR, include prior exposure to other viral infections leading to CD8+ T cell expansions, some of which could cross-react with the RPH epitope and therefore dominate the response from primary CMV infection (35).

The maintenance of TCR diversity across the population in the immune response to pathogen-derived peptides reduces the impact of sequence variation arising within these antigenic determinants. This report has demonstrated that a narrowing of the overall repertoire of BV genes in some individuals leads to an unexpected broadening of virus-specific T cell responses across the population by redirecting responses away from immunodominant TCRs. This enhanced virus-specific TCR diversity may be a major positive evolutionary influence that maintains inactivating polymorphisms and deletions in the TRB locus at high frequency across most human ethnic groups.

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Disclosures

The authors have no financial conflicts of interest.

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