Immunoglobulin Kappa Chain Receptor Editing in Systemic Lupus Erythematosus

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Abstract

To determine whether receptor editing of V<sub>k</sub> genes was involved in the pathogenesis of systemic lupus erythematosus (SLE), the usage of V<sub>k</sub> and J<sub>k</sub> gene elements from individual peripheral CD19<sup>+</sup> B cells obtained from a patient with untreated SLE was examined. No differences in the V<sub>k</sub> and J<sub>k</sub> gene usage in the nonproductive gene repertoire of this SLE patient were noted compared with the distribution of genes found in normal adults. However, an increased usage of J<sub>k</sub>5 containing segments, and a significant overrepresentation of the V<k>1</k> and V<k>4</k> families, especially the L15, O14/O4, and B3 genes characterized the productive V<sub>k</sub> gene repertoire of the SLE patient. Furthermore, J<sub>k</sub>5-containing V<sub>k</sub> gene rearrangements in the productive but not the nonproductive repertoire manifested significantly fewer mutations compared with V<sub>k</sub> genes recombined with J<sub>k</sub>1-4. These data are consistent with the conclusion that receptor editing of V<sub>k</sub> is much more apparent in this SLE patient than in normals and suggest that a deficiency in this means to counteract the emergence of autoimmunity is not an essential feature of SLE. (J. Clin. Invest. 1998. 102:688–694)

Key words: V<sub>k</sub> rearrangements • SLE • autoimmune diseases • receptor editing • B lymphocytes • generation of diversity

Introduction

Systemic lupus erythematosus (SLE) is the prototype of a systemic autoimmune disease characterized by B cell hyperreactivity and the production of a variety of autoantibodies (1). Although knowledge about the autoantibodies produced by SLE patients and their cognate autoantigens is increasing, the molecular basis of the induction of autoimmunity remains enigmatic. The potential roles of molecular processes and subsequent selective influences in the generation of autoreactive B cells in SLE have not been fully delineated. Immunoglobulin genes are assembled during early B cell development by the recombination of variable (V), diversity (D) and joining (J) elements in the bone marrow by a lymphocyte specific V(D)J recombinase (2, 3). In the bone marrow, expression of one membrane-bound B cell receptor (BCR) extinguishes subsequent rearrangements by downregulation of the expression of recombination activating genes (RAG) 1 and RAG2 (4). However, some immature B cells expressing self-reactive BCRs retain or reexpress sufficient RAG activity to replace those autoreactive receptors by continued Ig gene recombination (receptor editing) and thereby survive negative selection (5, 6). In the periphery, exposure to exogenous antigen can stimulate somatic hypermutation and also reexpression of RAG1 and RAG2 in germinal centers (7–9). If the mutational process generates an autoreactive BCR, additional receptor editing in the secondary lymphoid organs could potentially replace the autoreactive BCR and permit the survival of the B cell.

The possibility that deficiencies in central or peripheral receptor editing could play a role in generating autoimmunity has been suggested (10–14), but only a small number of studies have examined this hypothesis directly. Thus, Bensimon et al. (15) analyzed clones obtained from SLE patients and noted an overusage of J<sub>k</sub> proximal V<k>1</k> genes and preferential use of J<sub>k</sub> elements proximal to V<k>2</k> and suggested that receptor editing in SLE might be defective. In addition, a lack of receptor editing of V<sub>k</sub> rearrangements using the V<sub>k</sub> gene, A30, and Jc2 and encoding anti-dsDNA antibodies has been suggested to occur in patients with SLE and nephritis (13). These conclusions, however, are only inferential, and little direct evidence of defects in receptor editing in SLE patients has been provided. Moreover, the use of J<sub>k</sub> distal V<k>1</k> genes in some autoantibodies of SLE patients (16, 17) has suggested that receptor editing might be intact in these patients. Therefore, it is not clear whether receptor editing is intact or defective in SLE patients.

In the current study, we tested the hypothesis that receptor editing is defective in SLE patients by profiling the distribution of V<sub>k</sub> and J<sub>k</sub> genes in individual B cells of a patient with early, untreated SLE. Evidence of <k>κ</k> chain gene receptor editing was sought by comparing the distribution of V<sub>k</sub> and J<sub>k</sub> gene usage with that of normal donors (18). The data provide clear evidence that receptor editing was intact in this SLE patient and more apparent than that found in normals. The data therefore challenge the hypothesis that receptor editing is uniformly defective in patients with SLE.

Methods

Patient material. B cells were obtained from a 54-year-old Hispanic man with SLE, which was previously undiagnosed. Of note, his sister had SLE for 12 years. The primary care physician treated the patient with hydroxychloroquine for 8 d because of evolving subacute cutaneous lupus erythematosus (SCLE)–like lesions in sun-exposed areas, but no other therapy had been administered. Additional clinical

1. Abbreviations used in this paper: BCR, B cell receptor; RAG, recombination activating gene; SCLE, subacute cutaneous lupus erythematosus; V(D)J, variable, diversity and joining.
symptoms were increased fatigue, intermittent episodes of fever, malar rash and arthralgias of the proximal interphalangeal joints. Physical examination showed a typical butterfly rash and hyperkeratotic lesions of SLE. Mild proteinuria was evident with 300–500 mg of protein per day. Serologically, the ANA titer was 1:2,560 (speckled pattern), with antibodies to Ro, La, and RNP present. Anti-dsDNA antibodies were not present. White blood cell count was 3.8 × 10^3/μl with 20% lymphocytes. Complement factors C3 (62.6 mg/dl; normal: 65–203) and C4 (< 10 mg/dl; normal: 16–54) were reduced. Taken together, the patient fulfilled the revised criteria for classification of SLE (19).

Preparation of PBMC. PBMC were prepared from 50 ml of anticoagulated peripheral blood by centrifugation over ficoll hypaque gradients. Thereafter, 10 × 10^7 PBMC were stained using FITC-labeled anti–human CD19 (Sigma Chemical Co., St. Louis, MO) according to a previously described protocol (20).

FACS sorting and PCR amplification. 276 individual CD19+ B cells were sorted into wells of 96-well plates (Robbins Scientific, Sunnyvale, CA) by using a FACS® Star Plus flow cytometer with an automated single-cell deposit unit (Becton Dickinson, San Jose, CA), as described previously (20, 21). 12 wells (4 per plate) that received no cells served as negative controls. Rearranged VκJκ genes were then amplified as described (18). The PCR amplification included a primer extension preamplification (20) and subsequent nested PCR steps (18). After column purification of PCR products (GenElute Agarose Spin Column; Supelco, Bellefonte, PA), all PCR products were directly sequenced using the ABI Prism Dye Termination Cycle Sequencing Kit (Applied Biosystems, Inc., Foster City, CA) and analyzed with an automated Sequencer (ABI Prism 377; Applied Biosystems, Inc.). Sequences were analyzed using the V BASE Sequence Directory (22) to identify the respective germline gene. For the identification of the underlying germline segments, the software programs GeneWorks (release 2.45; IntelliGenetics Inc., Mountain View, CA) and Sequencer (Gene Codes Corp., Ann Arbor, MI) were used.

VκJκ rearrangements from two healthy normal male donors (26 years old and 45 years old) that had been published previously (18) were used for comparison. Both the nonproductive and productive repertoires of these two normal, age disparate donors exhibited a comparable usage of Vκ and Jκ gene elements.

The methodology used made it possible to amplify Ig gene rearrangements from peripheral B cells and, thereby, avoid biases inherent in analyzing cell lines or cDNA libraries (18, 21). Since genomic DNA was amplified, productive as well as nonproductive Vκ rearrangements could be amplified, sequenced, and analyzed. Analysis of the nonproductive repertoire is especially important in assessing the immediate product of the V(D)J rearrangement process or the impact of somatic hypermutation, as the nonproductive rearrangements could be amplified, sequenced, and analyzed. Further analysis of the error rate of somatic hypermutation, as the nonproductive rearrangements may be expected based upon the number of genes in the genome (18). The χ² test was used to compare the usage of Vκ and Jκ elements in the SLE patient and normals. Where indicated, the Bonferroni correction was applied to consider the influence of multiple variables (26). P values < 0.05 were considered to be statistically significant.

Results

76 VκJκ gene rearrangements were obtained from the 276 sorted individual B cells (accession numbers EMBL Data Bank AJ223638-AJ223713). These included a total of 59 productive and 17 nonproductive Vκ rearrangements. The nonproductive Vκ rearrangements failed to maintain the reading frame into the J segment. Most wells had a single Vκ rearrangement per well (56 out of 76, 73.7%). These included 44 productive and 12 nonproductive Vκ rearrangements. In five cases, two productive (8.9%) rearrangements and in five cases, one productive and one nonproductive (8.9%) rearrangement per well were detected. No well contained more than two Vκ rearrangements.

Vκ gene usage in SLE. The distribution of the usage of particular Vκ families is shown in Fig. 1. Members of the Vκ7 family were found neither in the SLE nor in the normal repertoire.

![Figure 1. Distribution of Vκ families in an SLE patient compared with normals. (*, P < 0.01, significantly different than predicted from its presence in the genome; goodness of fit χ² test). Brackets indicate significant differences between Vκ usage in the productive repertoire of normals and the SLE patient (χ² test).](image-url)
toire, whereas Vκ5 and Vκ6 genes were not detected in SLE. It should be noted that the usage of Vκ1 and Vκ4 family members was significantly more frequent in the productive repertoire of the SLE patient compared with the normals ($P < 0.01$ and $P < 0.02$, respectively, $χ^2$ test). Although Vκ2 and Vκ3 families were used less often in the productive SLE repertoire, the differences in frequencies of these families compared with the normals were of borderline significance ($Vκ2 P = 0.05$, $Vκ3 P = 0.05$). However, when the usage of particular Vκ families in the SLE patient was compared with the expected frequency based on random usage, the Vκ2 family was found to be significantly underrepresented in the SLE patient (8% compared with the expected 22.5%; $P < 0.01$). Moreover, as suggested above, the Vκ4 family, with the single gene, B3, occurred significantly more often than expected by random chance (14% vs. 2.5%; $P < 0.001$, goodness of fit $χ^2$ test). By this analysis, no significant differences were noted for the nonproductive rearrangements of the SLE patient, although the overrepresentation of Vκ1 genes (65%) suggests a molecular preference to rearrange these genes in SLE.

Distribution of individual Vκ genes in B cells from SLE. As shown in Fig. 2, the distribution of individual Vκ genes in the SLE patient and in the normal donors showed some differences in the productive and nonproductive repertoires. When the usage of particular Vκ gene segments by the SLE patient was compared with the normals, B3 (14%; $P < 0.02$), O14/O4 (10%; $P < 0.001$), and L15 (5%; $P < 0.001$, $χ^2$ test) were found to be significantly overrepresented in the productive SLE repertoire. In the nonproductive repertoire of the patient, A30 (24%; $P < 0.001$), L8 (12%; $P < 0.001$), L15 (12%; $P < 0.001$), and L25 (6%; $P < 0.001$) were significantly more frequent than in normals. The occurrence of some infrequently used Vκ genes (B2, L11, L10, L9, L5, L4, L2, L1, A26, A23, A21, A19, A18, O11/O1, A4, A7, A11, L19, L20, L23, and L24) in the normal donors (18) was not significantly different than that found in the SLE patient. The significant overrepresentation of the Vκ1 family gene, L15, in both the productive and nonproductive SLE repertoire is noteworthy. Finally, the Vκ1 family member, A30, was significantly overrepresented in the nonproductive rearrangements of this SLE patient ($P < 0.001$, $χ^2$ test) and exclusively rearranged with Jκ2. Similar differences between the distribution of this Vκ gene in productive and nonproductive repertoires were also found in normals (data not shown).

Comparison of the usage of the Jκ proximal and Jκ distal cassette. Because of a gene duplication event during phylogeny, the Vκ locus is composed of two cassettes of genes (27). The Jκ proximal cassette is orientated so that most rearrangements occur by deletion, whereas the Jκ distal cassette is arranged in the opposite orientation and recombination proceeds by inversion. Based upon the assumption that receptor editing might lead to greater usage of Vκ genes from the Jκ distal cassette, the frequency of these genes in the productive repertoire of the SLE patient was examined and compared with their presence in the nonproductive rearrangements. In the nonproductive repertoire of the SLE patient, 12 out of 17 Vκ (70.6%) genes belonged to the Jκ proximal cassette, and 3 out of 17 (17.6%) were from the Jκ distal cassette. Two Vκ genes (11.8%; L25 or L10 and O14 or O4) could not be ascribed to either of these regions. In the productive repertoire, 34 out of 59 (57.6%) Vκ genes were part of the proximal, whereas 5 out of 59 (8.5%) Vκ elements were part of the Jκ distal cassette. In this group of rearrangements, 20 genes (33.9%; O18 or O8, O14 or O4, and O12 or O2) could not be definitively assigned. Despite the comparable use of the Jκ distal cassette of Vκ genes by productive and nonproductive rearrangements, further analysis indicated that the productive repertoire of the SLE patient was indeed biased toward the use of Jκ distal Vκ genes. This was noted, when Vκ genes were divided into A17 proximal and A17 distal gene groups (A17 is $\sim$380 kB distal from Jκ1). There was no significant difference in the usage of A17 distal Vκ genes in the nonproductive repertoire of the SLE patient and normals (29.4% vs. 23.2%, $P = 0.56$). However, the difference in the usage of A17 distal Vκ genes in the productive repertoire of the SLE patient (42.3%) compared with that found in the normals (19.6%) was highly significant ($P < 0.001$, $χ^2$ test). Despite the preferential usage of the Jκ distal Vκ genes, the most Jκ proximal gene, the single Vκ4 family member, B3, was also overrepresented in the productive repertoire of the SLE patient compared to the normals (14% vs. 5%, $P < 0.02$).

Jκ gene usage in SLE. The distribution of the rearranged Jκ elements in the SLE patient is shown in Table I. Most notably, the usage of the Vκ distal Jκ5 segment was significantly in-

![Figure 2](image-url)
increased in the productive rearrangements of the SLE patient, with 36% of VkJk rearrangements using this element. In contrast, only 12% of the nonproductive rearrangements used this Jk element ($P < 0.005$, $\chi^2$ goodness test with Bonferroni correction). Furthermore, the usage of Jk3 ($P < 0.005$) and Jk4 ($P < 0.005$) was significantly less frequent in the productive SLE repertoire than expected by chance alone. Overuse of Jk5 in the productive repertoire of the SLE patient was confirmed by comparison with the normal donors. A significantly greater usage of Jk5 in the productive VkJk rearrangements of the SLE patient was observed (36% vs. 11%; $P < 0.001$, $\chi^2$ test), whereas Jk4 was used significantly less in the productive SLE repertoire (2% vs. 17%; $P < 0.001$). Comparison of the usage of the remaining Jk elements revealed no significant differences between the SLE patient and normals.

**Mutational analysis between Jk5- and Jk1-4-using Vk rearrangements.** Productive Jk5-using rearrangements from the SLE patient were found to use B3 and the A17 distal Vk elements O12/O2, O14/O4, and O18/O8 predominantly (Fig. 3). Moreover, the frequencies of mutations of the Vk rearrangements using Jk5 on the one hand or Jk1–4 on the other were significantly different (Table II). Thus, productively rearranged Vk genes using Jk5 contained significantly fewer mutations (frequency 1.99%; 99 mutations per 4,979 bp) than Jk1–4–using Vk rearrangements (frequency 3.08%; 280 mutations per 9,077 bp; $P < 0.001$, $\chi^2$ test). Similarly, when the A17 distal Vk genes (O12/O2, O14/O4, and O18/O8) and the B3 gene were analyzed for their mutational frequencies, Jk1–4–containing Vk rearrangements were mutated significantly more (frequency 3.1%; 79 mutations per 2,506 total bp) than the rearrangements using Jk5 genes (frequency 1.6%; 69 mutations per 4,275 bp; $P < 0.001$). Of importance, Jk5-using gene rearrangements manifested a high frequency of mutations in the nonproductive repertoire, indicating that Vk/Jk5 rearrangements could be subjected to mutations.

**Discussion**

The results of the current study suggest that peripheral B cells of this SLE patient receptor edit at the Vk locus more actively than previously noted in normals. This was manifested by deviation in the distribution of both Vk and Jk elements in the productive but not in the nonproductive repertoire, so that the frequencies of both the Jk distal Vk elements and the Vk distal Jk segment were increased. That receptor editing leading to these deviations occurred in secondary lymphoid organs after the mutational process had been initiated is indicated by the significantly lower mutational frequencies of rearrangements using these gene elements. These results imply that rather than being defective, peripheral receptor editing is markedly active in this patient with SLE. The capacity to bind autoantigens has been shown to emerge during immune responses to conventional exogenous antigens by somatic hypermutation of Ig genes with no intrinsic autoantibody activity (28–32). Moreover, somatic hypermutation of Ig genes with autoantibody specificity can increase the avidity of autoantibodies (33–35). Either process could provide the impetus for receptor editing in secondary lymphoid organs after initiation of somatic hypermutation. Alternatively, increased receptor editing may have been induced in this SLE patient to replace Ig genes that became defective in antigen binding or expression as a result of somatic hypermutation (23, 24).

Although Ig heavy chains (34, 36) have been shown to contribute to autoantibody binding, the important influence of light chains for autoantibody binding has been repeatedly emphasized (13, 16, 17, 35). Thus, the current evidence of receptor

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**Table I. Distribution of Jk Gene Usage in SLE**

<table>
<thead>
<tr>
<th>Jk</th>
<th>SLE</th>
<th>Normals</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Nonproductive</td>
<td>Productive</td>
</tr>
<tr>
<td></td>
<td>$n$</td>
<td>%</td>
</tr>
<tr>
<td>Jk1</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>Jk2</td>
<td>9*</td>
<td>53</td>
</tr>
<tr>
<td>Jk3</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Jk4</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Jk5</td>
<td>2</td>
<td>12</td>
</tr>
</tbody>
</table>

*One Jk gene productively rearranged with Vk O12/O2 could not be ascribed as a specific segment and therefore was not considered in this analysis. $P < 0.005$, significantly different than the number expected by random chance ($\chi^2$ goodness of fit test with Bonferroni correction). $\chi^2$ goodness of fit test with Bonferroni correction. **Significant difference between the usage of Jk4 ($P < 0.002$) and Jk5 ($P < 0.001$) genes, respectively, in the productive SLE repertoire compared with normals ($\chi^2$).
Table II. Comparison of the Mutational Frequencies between Vk Gene Rearrangements That Use Jk5 and Those Using Jk1-4

<table>
<thead>
<tr>
<th>Rearrangements</th>
<th>Nonproductive Mutations (n)</th>
<th>Total bp</th>
<th>Mutational Frequency (%)</th>
<th>Productive Mutations (n)</th>
<th>Total bp</th>
<th>Mutational Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jk1-4</td>
<td>109</td>
<td>3655</td>
<td>2.98*</td>
<td>280</td>
<td>9077</td>
<td>3.08*</td>
</tr>
<tr>
<td>Jk5</td>
<td>37</td>
<td>399</td>
<td>9.27*‡</td>
<td>99</td>
<td>4979</td>
<td>1.99*‡</td>
</tr>
<tr>
<td>Total</td>
<td>146</td>
<td>4054</td>
<td>3.60†</td>
<td>379</td>
<td>14056</td>
<td>2.70†</td>
</tr>
</tbody>
</table>

*P < 0.001, significant difference in the mutational frequency between Jk1-4 and Jk5 using rearrangements in the productive and nonproductive repertoire (χ² test). ‡P < 0.002, significant difference between the mutational frequency of productive and nonproductive Vk rearrangements (χ² test).

editing of kappa light chains implies that this process in SLE patients might be driven by the emergence of autoantibodies or increased avidity of autoantigen binding from the activation of the mutational process in secondary lymphoid organs.

Of note, the distribution of Vk gene family usage found in the nonproductive repertoire of the SLE patient, although limited, was similar to that found in normals. Furthermore, usage of Jk elements in the nonproductive Vk repertoire was also similar to that found in the normals. This suggests that there are no apparent differences in molecular processes that generate the Vk gene repertoire in this patient compared with that involved in the normal adult repertoire. Importantly, a molecular preference to rearrange Jk5 in SLE was not found, implying that the increased use of Jk5 in the productive rearrangements of the SLE patient related to events that occurred after VvJk rearrangement and requiring expression of a κ chain protein. This bias could relate to a form of positive selection not observed in normals. Alternatively, and more likely because of the Vv distal location of Jk5, the diminished frequency of mutations in Jk5 containing rearrangements and the discrepancy in this finding between normals and the SLE patient, the overrepresentation of Jk5 could result from receptor editing in secondary lymphoid organs after induction of somatic hypermutation.

It is interesting to note that there was no overrepresentation of the single member of the Vc4 family, B3, in the nonproductive rearrangements, although this gene was clearly overrepresented in the productive repertoire of the SLE patient. The current data indicate that biased expression of B3 in this SLE patient did not result from an abnormally biased recombination process, but rather from events that occurred after recombination and were dependent on expression of a κ chain protein. B3 is the most Jk proximal gene and its overrepresentation in the productive repertoire could be the result of positive selection. However, B3 frequently was rearranged to Jk5 (three out of eight times), and when it was rearranged to Jk5, it contained less mutations than when it was rearranged to Jk1-4 (2.4% vs. 3.2%). These results imply that some of the overrepresentation of B3 in the productive repertoire of this SLE patient might also result from receptor editing in secondary lymphoid organs. B3 would be available for receptor editing on the unarranged Vk locus as well as on the same chromosome when the initial rearrangements involved Vk genes of the distal cassette known to undergo rearrangements by inversion (27). In this latter circumstance, B3 would be retained and oriented so that it can rearrange by deletion in secondary lymphoid organs. Of importance, the B3 gene has been shown to encode for autoantibodies including the anti-dsDNA specific idiotype F4- (37) suggesting that receptor editing to the B3 gene may contribute to autoantibody formation in some circumstances.

It is interesting to note that Jc4 genes were detected less frequently in this SLE patient, although Jc4 has been reported to be frequently used for murine anti-dsDNA antibodies (38) as well as for a pathogenic 16/6 idiotypic positive human anti-DNA antibody (3F7-8; 39), and other human anti-dsDNA antibodies (37) and for anti-Ro antibodies (40). In this circumstance, autoantibodies might arise despite extensive negative selection and/or receptor editing of VkJk rearrangements including Jc4. Thus, autoantibodies in SLE might arise from VkJk rearrangements that are either incompletely deleted by receptor editing or alternatively introduced by the process of receptor editing.

Based upon the comparison with the productive Vc repertoire of the normal donors, receptor editing appeared to be greatly enhanced in this SLE patient. In transgenic animals expressing autoantibody encoding transgenes, receptor editing has been shown to rescue B cells by providing an alternative nonautoimmune B cell receptor, often leading to a marked skewing toward Jk5 expressing Vk gene products (10, 11, 41, 42). These findings have led to the conclusion that receptor editing at the κ locus plays a major role in rescuing autoimmune B cells from deletion (10). It has also been suggested that defects in receptor editing may play a role in the etiology of SLE (12–15). Contrary to this conclusion, however, the current data suggest that this rescue mechanism is intact and even exaggerated in this SLE patient, implying that defects of receptor editing do not routinely account for the emergence of autoimmune binding B cells.

The apparent exaggerated degree of receptor editing in this SLE patient has implications concerning the etiology of this autoimmune condition. The remarkable usage of receptor editing may merely reflect a more extensive degree of B cell stimulation than that found in normals. In this regard, more extensive proliferation of B cells with the generation of more memory B cells may predispose to increased use of Jk5 in the expressed repertoire. This seems to be unlikely to explain the current findings, however, as normal memory cells defined, by the presence of mutated Vk rearrangements, show no preference for the use of Jk5 (data not shown). It is more likely that the SLE patient used receptor editing as a means to delete Ig receptors that might have developed autoantibody specificity as a result of somatic hypermutation. Since, however, the patient exhibited a number of autoantibodies despite extensive receptor editing, the data suggest that this mechanism was insufficient to prevent autoimmunity. The results therefore suggest that the drive for ongoing B cell stimulation may overwhelm the capacity of receptor editing to prevent autoimmunity.

Studies using transgenic mice have examined receptor editing in B cells with germline encoded autoimmune Ig chains (10–12, 41, 42). However, reactivation of RAG genes and recombination in the periphery (7–9) have been documented and suggest a mechanism whereby autoantibodies that arise as a result of somatic hypermutation can be edited. This mechanism appears to be robust in SLE. The results concerning the function of receptor editing of germline encoded autoantibod-
ies in this patient are less clear. One indication that this might be intact in this SLE patient is the evidence of deletion of A30/Jk2 rearrangements that have been shown to be deleted in normals by a mechanism that may relate to receptor editing (18). Although the current study did not prove that receptor editing deleted A30/Jk2 rearrangements from the productive repertoire of this SLE patient, a previous study had suggested that this is the mechanism in normals (13). Although a previous analysis suggested that A30 might be defective and not rearranged in some SLE patients (13), the patient studied here rearranged this gene frequently and always to Jk2 but deleted it normally. The retention of this deletional editing function may explain the lack of anti-dsDNA antibodies in this patient as the product of this gene is a frequent component of cationic anti-dsDNA antibodies (13, 43).

This study documents that receptor editing at the Vκ locus is used more apparently in a patient with untreated SLE than in normals. Despite this, autoimmunity emerged. Of note, however, this patient did not express anti-ds DNA antibody. These results suggest that receptor editing in this patient was not defective but rather active, although insufficient to prevent all autoimmunity. Therefore, receptor editing is not uniformly defective in SLE, whereas other mechanisms, such as clonal deletion or anergy, may be disturbed so as to allow the emergence of autoantibody formation.

Acknowledgments

The authors are grateful to Dr. H.-P. Brezinschek for helpful discussions, Dr. R.I. Brezinschek for assistance with the cell sorting, and Dr. A.C. Grammer for critical review of the manuscript.

This work was supported by National Institutes of Health grant AI 31229. T.D. is a recipient of a Deutsche Forschungsgemeinschaft grant (Do 491/2-1).

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