We have examined α/β V gene segment usage of peripheral blood CD4+ and CD8+ T cells, respectively, from patients with multiple myeloma and monoclonal gammopathy of undetermined significance, by using T cell receptor (TCR) for antigen monoclonal antibodies (MoAbs). In 7 of 16 patients we found an increase in the usage of various TCR V gene segments. The expansion was confined to either the CD4+ or the CD8+ T-cell subset, except for one patient where an abnormal pattern was observed both within the CD4+ and CD8+ T-cell subsets. In one patient 47%, and in another patient 30% of the CD8+ lymphocytes reacted with αV12.1 and βV8.7 antibodies, respectively. In two other patients 29% and 40% of the CD4+ lymphocytes reacted with βV6.7 and βV8.1 antibodies, respectively. We conclude that T cells with a predominant V gene usage is a frequent feature in patients with abnormal clonal B cells of malignant or benign types. T- and B-cell populations are normally clonally linked in regulatory circuits. An abnormal proliferation of B cells might therefore induce, or be regulated by, an expansion of clonal T cells, as suggested by the present results.

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THE CELLS OF THE IMMUNE system capable of displaying clonal expansions, based on specific antigen recognition, contain as dominating subsets the B and T lymphocytes. A delicate balance is assumed to exist within these populations where changes in one subpopulation may lead to corresponding alterations in the size and/or functions of other subgroups. Abnormalities in the composition in one subset of lymphocytes may accordingly induce secondary abnormalities in other subpopulations.

T cell precursors migrate from the bone marrow to the thymus where the thymocytes begin to mature and express the α/β T cell receptor for antigen (TCR). Through positive and negative selection, CD4+ T cells become restricted to major histocompatibility complex (MHC) class II, and CD8+ T cells to MHC class I. These “educated” CD4+ or CD8+ T cells enter the periphery, where they, after encountering an antigen in a MHC restricted manner, might be induced to become effector cells or long-lived memory cells. The high variability of the α/β TCR, calculated to be in the order of 10^11, is achieved through the rearrangement of V, J, D (only β) gene segments. Also junctional and N-linked diversity as well as multiple reading frames for D segments adds to the variability of the TCR. For the α chain >50 and for the β chain >70 V gene segments have been described. A dominant usage of certain β V gene families in normal human peripheral T cells has been demonstrated. We have also recently found a differential usage of specific α/β V genes between CD4+ and CD8+ peripheral T cells.

In different abnormal situations a perturbation of this clonal T-cell balance has been documented. T-cell leukemia/lymphomas, certain autoimmune diseases, and superantigen related disorders are examples where, in different ways, the presence of T-cell clonality may have a negative impact for the individual.

Multiple myeloma (MM) and monoclonal gammopathy of undetermined significance (MGUS) represent malignant and benign clonal expansion respectively of B lymphocytes and plasma cells. In B-cell malignancies, parallel clonal T-cell populations both in animal and human systems have been shown. Such clonal T cells may exert beneficial or nonbeneficial regulatory functions on the malignant B-cell clone and may be part of an immune response against the tumor cells. In monoclonal gammapathies a derangement of various T lymphocyte subpopulations has been described. Relative and absolute numbers of CD8+ lymphocytes were increased, a fact that was more pronounced in patients with active disease. Within such CD8+ populations human leukocyte antigens (HLA)-DR expressing lymphocytes binding the immunoglobulin (Ig) idotype were noted. A selective loss of CD4+/CD45R+ (suppressor/cytotoxic inducer) cells has also been found.

Different methods can be applied to analyze the degree of clonal dominance in a polyclonal T-cell population. As one criterion for clonality the preferential single V gene usage has been practical. With the method of Southern, clonality was assessed by probing for gene rearrangements representative for the β-chain of the T cell receptor loci. Using probes against the constant gene, or with probes against a panel of V gene segments, dominating V gene usage could be demonstrated. More recently a PCR based quantitative methodology has been applied to demonstrate a restricted V gene usage. It is also possible to directly identify a T cell displaying a defined V gene product within its TCR using a MoAb. This technology does not only allow for a precise estimation of the percentage of cells with such a feature but may also permit selective enrichment or
T CELLS IN MYELOMA AND MGUS

The question we addressed is in what way an abnormal clonal B-cell population might affect the clonality of peripheral T lymphocytes. Using double-staining immunofluorescence (IFL) analysis of CD4+ and CD8+ T cells, respectively, with a panel of TCR MoAbs detecting various αV or βV gene products, we have found a predominant T-cell V gene usage in patients with MM and MGUS. Results indicate that abnormal clonal B-cell populations, of clinical benign or malignant types, are dependent on or induce a selective T-cell expansion. If further functional characterization shows a positive and/or negative impact of such T cells on the B cell diseases analyzed, manipulation of these T-cell populations might be a therapeutic possibility.

MATERIALS AND METHODS

Patients. Thirteen untreated patients with MM were studied. The diagnostic criteria have been described earlier. The clinical staging system according to Durie and Salmon was used. Three patients had MGUS as defined previously.

Control population. Peripheral blood from 24 blood donors was used as controls.

Antibodies. Eight MoAbs against the variable part of the TCR α or β chains were used: LC4 (βV5.1),16,19 IC1 (βV5.2 +3),20 W112 (βV5.3),21 OTI145 (βV6.7),22 16G8 (βV8.1),21 and S511 (βV12.1)16 (all provided by T Cell Sciences, Cambridge, MA), F1 (αV2.3)16 and 6D6 (αV1.2) (DerSimonian et al, submitted). The OKT3 (CD3) hybridoma was obtained from American Type Culture Collection (ATCC), Rockville, MD, and the MoAb was produced in our laboratory. Fluoresceinisothiocyanate (FITC) conjugated F(ab')2 fragments of rabbit anti-mouse Ig was purchased from Dakopatts A/S, Glostrup, Denmark. Phycoerythrin (PE) labeled Leu-3a (CD4) and Leu-2a (CD8) were purchased from Becton Dickinson, Mountain View, CA. Normal mouse serum (NMS) was obtained from adult BALB/c mice and used at a dilution of 1:500.

Isolation of lymphocytes. Mononuclear cells were isolated from heparinized blood by Ficoll-Hypaque (Pharmacia, Uppsala, Sweden) gradient centrifugation.

Immunofluorescence and cytometry. The test was performed at +4°C. Cells were incubated for 30 minutes with unlabeled antibody, washed twice in phosphate-buffered saline (PBS), incubated with FITC conjugated F(ab')2, fragments of rabbit anti-mouse Ig for 30 minutes and washed three times in PBS. NMS diluted 1:500 in PBS was added to block free rabbit anti-mouse reactivity. After 10 minutes Leu-2a-PE and Leu-3a-PE, respectively, were added, incubated for 20 minutes, and the cells were washed twice. The samples were analyzed by a FACScan flow cytometer (Becton Dickinson) and a Hewlett Packard 300 computer (Palo Alto, CA). Lymphocytes were gated out live by forward and side scatter setting and 104 cells were analyzed. NMS was used as a negative control. Optimal compensation was set for green and orange fluorescence.

Definition of predominant V gene usage. The presence of a predominant V gene was defined as a value ≥ twice the upper normal range for that specific TCR MoAb. Values between the upper normal range and twice the upper normal range was considered as a slight increase but not a predominant V gene usage. These arbitrary limits were chosen not to overestimate the results.

RESULTS

Control donors. Twenty-four blood donors were used as controls. The percentage of cells reacting with the different TCR MoAbs within the CD4+3+ (γ/δ)-, CD8+3+ (γ/δ)-, and CD3+ (γ/δ)- populations respectively are shown in Table 1. The percent of cells stained by the different MoAbs varied. The total median percent of cells stained by the TCR MoAbs was 25.1% for CD3+ cells, 23.6% for CD4+ cells and 21.8% for CD8+ cells. Our panel of TCR MoAbs does accordingly cover roughly one fourth of the TCR α/β repertoire. An extended analysis of the V gene usage in normal donors is presented by us elsewhere.16 The reproducibility of repeated IFL tests using the same sample was good with negligible variations.

T cells in the blood of MM and MGUS patients. The results on individual TCR MoAb reactivities within the CD4+, CD8+, and CD3+ T cells, respectively, are depicted in Tables 2 through 4. Close to half of the patients (7 of 16) had T cells that predominantly used one or two V gene segments, as defined by a value ≥ twice the upper normal range (see Materials and Methods). An increase was seen both within the CD4+ or CD8+ populations. In patients 7, 10, 13, and 14, an accumulation of T cells using a specific αV or βV gene segment within the CD4+ population was noted (Table 2). In patients 3, 4, 6, and 14, a predominant usage of TCR V gene products of the CD8+ cells was found (Table 3). Accordingly, patient 14 had a predominant V gene usage both within the CD4+ and CD8+ subpopulations. In some individuals, as exemplified in Fig 1, close to half of the CD8+ T cells used the same V gene segment (47% of the CD8+ T cells used the αV12.1 gene as defined by the antibody 6D6) (DerSimonian et al, submitted).

In 9 of 16 patients an increase between the upper and twice the upper normal range was noted in one or more of the TCR/CD4 subpopulations while only one patient had a decrease (below the normal range) in more than one population (no. 14). In two patients (nos. 12 and 16) three cell populations staining for various TCR MoAbs were increased simultaneously. The opposite situation was noted for CD8+ cells where three patients had a small increase in one or two TCR MoAb stained cells, but five patients had a decreased TCR MoAb reactivity. This depression was pronounced in patients 1, 6, and 15, where three to five of the TCR MoAbs reacted below the normal range. Simultaneous to these depressions in patients 6 and 15, an increase

<table>
<thead>
<tr>
<th>TCR MoAb</th>
<th>% of CD4+ Cells</th>
<th>% of CD8+ Cells</th>
<th>% of CD3+ Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1 (α V2.3)</td>
<td>3.5 (2.6-5.6)</td>
<td>3.1 (2.6-10.0)</td>
<td>3.6 (2.6-5.6)</td>
</tr>
<tr>
<td>6D6 (α V12.1)</td>
<td>2.4 (0.7-3.3)</td>
<td>4.1 (1.1-15.8)</td>
<td>3.4 (1.3-5.5)</td>
</tr>
<tr>
<td>LC4 (β V5.1)</td>
<td>4.8 (1.8-6.1)</td>
<td>1.6 (0.3-3.8)</td>
<td>3.7 (1.9-5.0)</td>
</tr>
<tr>
<td>1C1 (β V5.2+5.3)</td>
<td>2.2 (1.6-3.5)</td>
<td>2.6 (1.1-15.1)</td>
<td>3.5 (2.1-8.7)</td>
</tr>
<tr>
<td>W112 (β V5.3)</td>
<td>0.8 (0.4-1.6)</td>
<td>0.8 (0.2-13.2)</td>
<td>1.3 (0.5-6.8)</td>
</tr>
<tr>
<td>OTI145 (β V6.7)</td>
<td>4.4 (0.3-8.8)</td>
<td>1.2 (0.2-12.3)</td>
<td>4.1 (0.3-7.8)</td>
</tr>
<tr>
<td>16G8 (β V8)</td>
<td>4.7 (3.1-15.7)</td>
<td>3.1 (1.4-9.3)</td>
<td>4.6 (2.9-10.0)</td>
</tr>
<tr>
<td>S511 (β V12)</td>
<td>1.9 (0.2-2.4)</td>
<td>1.2 (0.5-2.1)</td>
<td>1.8 (1.2-2.5)</td>
</tr>
</tbody>
</table>

Bold numbers represent median values. Values within the brackets define the range.
Table 2. Percent of CD4+ Peripheral Blood Lymphocytes Reactive With TCR MoAbs in MM or MGUS Patients

<table>
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<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Clinical Stage</th>
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<tr>
<td>1</td>
<td>MGUS</td>
<td></td>
<td>F1 6D6 LC4 1C W112 OT145 16G8 SB11</td>
</tr>
<tr>
<td>2</td>
<td>MGUS</td>
<td></td>
<td>2.8 4.3 3.9 3.7 1.2 4.3 7.3 2.1</td>
</tr>
<tr>
<td>3</td>
<td>MGUS</td>
<td></td>
<td>3.1 3.0 6.8 3.2 1.0 7.4 6.1 2.0</td>
</tr>
<tr>
<td>4</td>
<td>MM</td>
<td>I</td>
<td>5.7 3.3 5.3 1.9 1.1 6.9 5.0 1.8</td>
</tr>
<tr>
<td>5</td>
<td>MM</td>
<td>I</td>
<td>3.4 3.0 5.0 2.4 0.7 3.0 10.1 1.6</td>
</tr>
<tr>
<td>6</td>
<td>MM</td>
<td>I</td>
<td>6D6 2.2 6.7 ND ND ND ND 5.1 1.2</td>
</tr>
<tr>
<td>7</td>
<td>MM</td>
<td>II</td>
<td>12.4 1.8 5.1 3.0 1.1 3.1 4.1 2.3</td>
</tr>
<tr>
<td>8</td>
<td>MM</td>
<td>II</td>
<td>3.5 0.9 8.5 2.7 1.2 3.2 4.4 1.9</td>
</tr>
<tr>
<td>9</td>
<td>MM</td>
<td>II</td>
<td>3.8 2.8 6.7 3.6 1.1 0.8 5.3 2.4</td>
</tr>
<tr>
<td>10</td>
<td>MM</td>
<td>II</td>
<td>(2.0) 1.4 2.4 2.9 0.6 1.9 397 1.1</td>
</tr>
<tr>
<td>11</td>
<td>MM</td>
<td>II</td>
<td>3.4 4.4 5.8 2.7 0.8 4.4 5.7 2.2</td>
</tr>
<tr>
<td>12</td>
<td>MM</td>
<td>II</td>
<td>4.6 3.4 7.1 4.1 1.4 5.9 6.8 2.3</td>
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<tr>
<td>13</td>
<td>MM</td>
<td>III</td>
<td>3.7 1.6 4.6 2.8 0.9 5.2 4.9 5.1</td>
</tr>
<tr>
<td>14</td>
<td>MM</td>
<td>III</td>
<td>(2.2) 1.6 (1.6) (1.4) 0.7 28.5 (24) 0.9</td>
</tr>
<tr>
<td>15</td>
<td>MM</td>
<td>III</td>
<td>2.6 1.2 2.5 1.6 0.5 3.1 3.1 0.7</td>
</tr>
<tr>
<td>16</td>
<td>MM</td>
<td>III</td>
<td>4.0 4.2 4.8 3.7 0.7 11.6 5.2 2.4</td>
</tr>
</tbody>
</table>

Abbreviation: ND, not determined.

*Background reactivities (NMS) were < 0.1%. Bold numbers indicate a value twice the normal upper range; underlined numbers indicate a value between the upper and twice the normal range, and numbers within brackets indicate values that are below the normal range of the control population.

of a TCR MoAb reactivity was seen. In patient 1, no predominant V gene usage was seen, despite three depressed values, but such an expansion might be predicted to be located outside our detection limits.

For CD3 the pattern was similar to that of the combined results of CD4+ and CD8+ subpopulations, but as expected the extreme values were less pronounced (Table 4). Only 4 of 16 patients had values exceeding twice the upper control range. Also, the depressed reactivities were less abundant. In three of the seven patients with a predominant V gene usage we were able to reanalyze the patients after a 9-month interval. In patient 4, the usage of αV6.7 among the CD8+ T cells was reduced from 28.6% to 17.8% and the usage of βV5.1 in the CD8+ T-cell population was significantly reduced from 22.4% to 1.3%. Interestingly, patient 4, with an unchanged predominant V gene usage, had not received any therapy, while patients 7 and 14, with reduced T-cell clones, both were treated with melphalan during the interval.

DISCUSSION

In an earlier study, we presented evidence for the existence of predominant T-cell clones among the peripheral T-cell population in chronic B cell lymphocytic leuke-

Table 3. Percent of CD8+ Peripheral Blood Lymphocytes Reactive With TCR MoAbs in MM or MGUS Patients

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<td></td>
<td>4.4 1.2 (0.0) 4.1 0.3 0.7 (0.4) (0.1)</td>
</tr>
<tr>
<td>3</td>
<td>MGUS</td>
<td></td>
<td>2.2 3.1 2.2 1.2 0.5 1.1 2.3 2.2</td>
</tr>
<tr>
<td>4</td>
<td>MM</td>
<td>I</td>
<td>1.1 47.0 2.3 1.7 0.4 3.3 2.3 (0.3)</td>
</tr>
<tr>
<td>5</td>
<td>MM</td>
<td>I</td>
<td>0.9 6.4 1.4 1.9 0.9 34.0 15.6 0.9</td>
</tr>
<tr>
<td>6</td>
<td>MM</td>
<td>I</td>
<td>4.8 11.0 2.1 (0.8) 0.3 1.5 4.9 2.1</td>
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<tr>
<td>15</td>
<td>MM</td>
<td>III</td>
<td>(0.4) 4.7 2.3 (0.5) 0.3 0.1 14.5 (0.3)</td>
</tr>
<tr>
<td>16</td>
<td>MM</td>
<td>III</td>
<td>2.3 11.1 3.1 2.2 0.5 1.6 5.4 0.7</td>
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*Background reactivities (NMS) were < 0.4%. For explanations see Table 2.
T CELLS IN MYELOMA AND MGUS

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where clonaly expanded T cells were detected by the

mia and in smoldering myeloma. The methodology used,

related to the CD4' or CD8+ cell populations. With the

Southern blot analysis, did neither allow us to determine

the degree of clonality, nor to analyze if it was selectively

distinguished within these limits. Analyzing

compartment. The TCR MoAbs were specific for one or

more of the TCR V gene cell membrane products. Alto-

together they stained approximately 25% of the CD3+ blood
cells, which implied that we could identify a predominant V
gene usage only if it occurred within these limits. Analyzing

the normal V gene usage we found a biased distribution of
certain V gene segments, indicating the importance of

thymic selection mechanisms.

The results in this paper strongly suggest the presence of

a clonal T-cell expansion in association with clonal B-cell

expansion, confirming our initial observations (Wen et al) where clonally expanded T cells were detected by the

method of Southern in one patient with smoldering my-
eloma and in three patients with B-CLL. Those results

indicated that T cells with a predominant usage of V gene

segments have a limited junctional diversity. However, the

accumulation of T cells using a specific α or β V gene

segment does not prove that they represent a strictly clonal

cell proliferation with identical TCR gene rearrange-

ments.

We found evidence for a predominant usage of α or β V
gene segment products within the CD4+ and CD8+ blood

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1 of 3 MGUS patients. The predominant V gene usage was

left unchanged over time in one untreated MM patient (no.

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14) that received melphalan therapy. The cytostatic therapy

might have affected the T-cell population directly, or the

reduction of T cells could have been indirectly regulated by

an elimination of tumor cells. The fact that the present

battery of MoAbs only covered one fourth of the total TCR

repertoire, but 44% of the individuals were found to have

abnormal T-cell clones does allow the assumption that the

vast majority of individuals with abnormal B-cell clones do

have clonally expanded T cells. In none of the 16 patients

we, however, able to detect expansion of cells where both the αV

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vast majority of individuals with abnormal B-cell clones do

have clonally expanded T cells. In none of the 16 patients

we, however, able to detect expansion of cells where both the αV

gene products on the same cell

or βV gene products on the same chain in

the μ chain with

indicated that T cells with a predominant usage of V gene

segments have a limited junctional diversity. However, the

accumulation of T cells using a specific α or β V gene

segment does not prove that they represent a strictly clonal

cell proliferation with identical TCR gene rearrange-

ments.

We found evidence for a predominant usage of α or β V
gene segment products within the CD4+ and CD8+ blood

T-cell populations, respectively, in 6 of 13 MM patients and

1 of 3 MGUS patients. The predominant V gene usage was

left unchanged over time in one untreated MM patient (no.

4), while a reduction was noted in two patients (nos. 7 and

14) that received melphalan therapy. The cytostatic therapy

might have affected the T-cell population directly, or the

reduction of T cells could have been indirectly regulated by

an elimination of tumor cells. The fact that the present

battery of MoAbs only covered one fourth of the total TCR

repertoire, but 44% of the individuals were found to have

abnormal T-cell clones does allow the assumption that the

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ments.
presence of T cells with an unrevealed predominant V gene usage, which could not be identified with the present panel of TCR MoAbs.

A method using the polymerase chain reaction (PCR) to analyze a preferential βV gene usage has recently been published. With this technique a selective expansion of T cells expressing certain βV gene segments when exposed to different superantigens could be demonstrated. Also, a limited usage of αV genes in multiple sclerosis lesions has been documented. One advantage of the PCR method is that it can cover most of the human T cell V gene repertoire. However, the present methodology using TCR MoAb will not only allow for an identification of T cells with a defined V gene usage (within our limits of detection), but also has the advantage of providing tools for functional analysis and for therapeutic manipulations of selected T cells.

The functional impact of the present T cells, predominantly using different V gene segments, remains to be established. If specific for the corresponding idiotypic Ig molecules of the expanded B-cell clone, they may well express selective negative (helper) or positive (suppressor/cytotoxic) functions in relation to the individual. In the mouse myeloma system, specific T cells have been identified that suppress the proliferation and immunoglobulin secretion of the myeloma cells. Also, T helper cells with specificity for peptides from the V region of myeloma protein have been described. The existence of potential regulatory T cells might thus be of important clinical interest as these may be targets for immune manipulation.

REFERENCES

Predominant T cell receptor V gene usage in patients with abnormal clones of B cells

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