Targeting Human B-cell Malignancies through Ig Light Chain–Specific Cytotoxic T Lymphocytes

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Abstract

Purpose: The variable regions of Ig (idiotype, Id) expressed by malignant B cells can be used as tumor-specific antigens that induce humoral and cellular immunity. However, epitopes derived from Id that stimulate human CD8\(^+\) T-cell immunity are incompletely characterized.

Experimental Design: The clonal Ig VL of human myeloma cell line U266 and five primary B-cell tumors were sequenced, and peptides corresponding to the Ig VL region were tested for their ability to stimulate CTLs from 10 HLA-A\(^*\)0201–positive normal donors. The CTLs thus generated were tested against peptide-pulsed T2 cells and autologous tumor cells.

Results: Fourteen peptides derived from Ig light chain (VL) of U266 and primary B-cell tumors were used to generate 68 CTL lines that specifically produced IFN-\(\gamma\) when cocultured with peptide-pulsed T2 cells. These CTLs lysed peptide-pulsed T2 cell as well as U266 or autologous tumor targets in an HLA class I–dependent manner. Sequence analysis revealed shared VL T-cell epitopes in U266 and primary B-cell tumors, not previously reported within Ig heavy chain (VH) sequences.

Conclusion: This study thus identifies novel immunogenic CTLs epitopes from Id VL, suggests that they are naturally presented on the surface of B-cell malignancies, and supports their inclusion in next-generation Id vaccines. The ability to prime T cells derived from normal HLA-matched donors, rather than patients, may also have direct application to current strategies, designed to generate allogeneic tumor-specific T cells for adoptive transfer.

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Introduction

B-cell malignancies express unique variable region determinants in their surface Ig receptor (idiotype, Id) that can serve as tumor-specific antigens. Studies in mice and humans showed that humoral and cellular immune responses were induced following Id vaccination (1–4). We have previously shown that autologous Id protein can be formulated into an immunogenic antigen in lymphoma patients, by conjugation with a carrier protein, keyhole limpet hemocyanin (KLH), and administration with granulocyte macrophage colony-stimulating factor (GM-CSF) as adjuvant. Lymphoma-specific CD8\(^+\) T-cell responses were associated with achievement of molecular remissions (3). In human myeloma patients, T-cell responses specific for Id protein have generally been shown, suggesting immunogenicity of this tumor antigen (5). Finally, a randomized phase III clinical trial of an Id protein vaccine recently has shown prolonged remission duration in follicular lymphoma (FL) patients in first remission (6). However, the immunogenic epitopes derived from Id that stimulates CD8\(^+\) T-cell responses have been incompletely characterized, especially Id light chain (VL) determinants.

Despite the availability of new proteasome inhibitors and other targeted agents, disease relapse still remains a major problem for myeloma patients, and even high-dose therapy followed by autologous stem cell transplantation (SCT) in tandem does not seem to be curative for this disease (7). In contrast, allogeneic SCT following either myeloablative or reduced intensity conditioning has been shown to induce prolonged disease-free survival in a small percentage of patients, suggesting a possible graft-versus-myeloma (GVM) effect (8). Attempts to enhance the GVM effect by donor lymphocyte infusions (DLI) have resulted in an increased incidence of graft-versus-host disease (GVHD; ref. 9). Therefore, strategies to enhance the specific antitumor effect of the graft without increasing the risk of GVHD are needed to improve outcome in allotransplant recipients.

One novel strategy is to transfer highly enriched populations of tumor antigen–specific T cells from donor to

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Translational Relevance

Despite improvements in high-dose therapy followed by autologous stem cell transplantation (SCT), disease relapse still remains a major problem for B-cell malignancy patients, and even tandem autotransplants do not seem to be curative for these diseases. Allogeneic SCT following either myeloablative or reduced intensity conditioning has been shown to induce prolonged disease-free survival in a small percentage of patients, suggesting a possible graft-versus-myeloma effect. The ability to prime tumor-specific T cells derived from normal HLA-matched donors, rather than autologous patients, may have direct application to current adoptive transfer strategies already in clinical testing.

Materials and Methods

Human tumors
U266 myeloma cell line (HLA-A*0201/A3+) was obtained from American Type Culture Collection. HLA-A*0201 primary FL or chronic lymphocytic leukemia (CLL) tumors were purified from patient’s blood or spleen with HISTOPAQUE-1077 (Sigma) and B-cell isolation kit (Miltenyi Biotec). HLA-A*0201 primary plasma cell leukemia (PL) cells were isolated with CD138+ cell isolation kit (Miltenyi Biotec). All patients’ samples were collected before the administration of high-dose therapy or Id vaccination. This study was approved by the Institutional Review Board Committee, and informed consent was obtained in accordance with the Declaration of Helsinki.

Reverse transcriptase PCR of Id light chain cDNA
A total of 3 μg RNA was extracted from U266, and primary tumors were reverse-transcribed into cDNA with SuperScript III Kit from Invitrogen (catalogue no. 11745100). The highly variable region of Id light chain region was PCR amplified with primers from a published article (12). The PCR conditions were as follows: 94°C, 5 minutes, followed by 94°C, 30 seconds and 58°C, 30 seconds; 72°C, 45 seconds for 35 cycles; and 72°C, 9 minute. The PCR product was cloned into PCR2.1 TOPO vector (Invitrogen; catalogue no. K2000-01) and sequenced in the DNA core facility of MD Anderson Cancer Center.

Peptide synthesis and T2 binding
Peptides predicted to bind to HLA-A*0201 were synthesized to greater than 70% purity, dissolved in 100% dimethyl sulfoxide (DMSO; Sigma), and the binding affinity to HLA-A*0201 molecules was measured with T2 cells according to published methods (13). In brief, T2 cells were incubated with 50 μg/mL peptides and 3 μg/mL of β2-microglobulin (Sigma; catalogue no. M4890) for overnight. The cells were then washed and incubated with phycoerythrin (PE)-labeled anti–HLA-A0201 monoclonal antibody (mAb; clone BB7.2; BD Biosciences) for 30 minutes at 4°C. After washes and fixation, cells were analyzed for the levels of HLA-A2 expression by flow cytometry. The binding affinity of peptide was quantified according to the formula [(mean fluorescence with peptide – mean fluorescence without peptide)/mean fluorescence without peptide] × 100%. Influenza A virus M1 58-66 (GILGFVFTL) peptide was used as a positive control.

Generation of peptide-specific CTLs
The CTLs were generated from HLA-A*0201 normal donor peripheral blood mononuclear cells (PBMC) using reported methods (14). Briefly, PBMCs (1 × 10^5 cells/well) were incubated with 10 μg/mL peptide in quadruplicate in 96-well U-bottom microculture plates in 200 μL culture medium (50% AIM-V, 50% RPMI-1640, 10% human AB serum, and 100 IU/mL IL-2) and restimulated with peptide every 3 days. After 5 stimulations, T cells were stimulated with peptide-pulsed T2 cells and IFN-γ production was determined in supernatants by ELISA. CD8+ T cells were isolated from IFN-γ-producing cultures by magnetic-activated cell sorting and expanded by rapid expansion protocol (15). Influenza A virus M1 58-66 (GILGFVFTL) peptide was used as a positive control.

Cytotoxicity
U266 and primary tumor cells were labeled with ^51Cr, and standard 4-hour cytotoxicity assay was conducted. Anti-human HLA-ABC (clone W6/32; eBiosciences), anti-HLA-DR, DP, and DQ (clone TÜ39; BD Biosciences), and mouse IgG2a isotype control (eBiosciences; catalogue no. 16-4724-81) were used to determine HLA restriction. All assays were conducted in triplicate and repeated 3 times.

Intracellular cytokine staining assay
Effector T cells were mixed with T2 or antigen-presenting cells (APC) loaded with 10 μg/mL peptide in a 1:1 ratio. Two hours later, 5 μg/mL Brefeldin A (Sigma) was added to block the transfer of Golgi part. The staining of intracellular cytokine was carried out with BD Cytofix/Cytoperm Plus Fixation/Permeabilization Kit 12 hours later. A total of 10 μL mouse anti-human IFN-γ (clone 25723.11; BD Biosciences), mouse anti-human TNF-α (clone MAb11; BD Biosciences), mouse anti-human GM-CSF (clone 4H1; eBiosciences), mouse anti-human IL-4 (clone 8D4;
BD Biosciences), mouse anti-human IL-10 (clone JES3-9D7; eBiosciences), mouse anti-human IL-17 (clone eBio64DEC17; eBiosciences), and mouse anti-human CD8 (clone HIT8a; BD Biosciences) were added to the 100 μL effector T cells and stained for 30 minutes at 4°C in the dark. After 2 times washes in 1× Perm Buffer, the samples were analyzed by flow cytometry and the data were analyzed with CellQuest software or FlowJo.

Statistical analysis
The Student t test was used to compare various experimental groups. Unless otherwise indicated, the mean average and SDs of triplicate wells are shown.

Results
Generation of Id VL-specific T-cell lines from normal donors
As a model, we used peptides derived from the VL of human U266 myeloma cell line to generate CTLs. Eighteen peptides from λ VF of U266 were selected on the basis of the predicted binding affinity to HLA-A*0201 (http://www.bimas.cit.nih.gov/molbio/hla_bind/). Most peptides showed modest binding capacity to HLA-A*0201 (http://www-immuno.cancernet.ca/IMGT_vquest/vquest?livret=0&Option=humanIg). Most peptides predicted binding affinity to HLA-A*0201 (Table 1), confirming their immunogenicity in general normal donors. Using intracellular cytokine assay, we showed that CTLs produced IFN-γ, TNF-α, and GM-CSF but not IL-4, IL-10, or IL-17 cytokines (Fig. 1C).

Cytotoxicity of Vs peptide–specific donor T cells
We expanded peptide-specific CTLs and assayed for cytotoxicity against peptide-pulsed T2 cells and primary tumors. Both U266 peptide–specific CTLs (Fig. 2A) and CTLs generated against Vs peptides from primary tumors (Fig. 2B) efficiently lysed Id but not control peptide–pulsed T2 targets.

Table 1. Characteristics of Vs T-cell epitopes from U266 and primary B-cell tumors
<table>
<thead>
<tr>
<th>Tumor source</th>
<th>Peptide Variable region a</th>
<th>Subfamily b</th>
<th>Start position a</th>
<th>Sequence b</th>
<th>Length</th>
<th>Predictive binding c</th>
<th>Mean fluorescence d</th>
<th>Shared tumors a</th>
</tr>
</thead>
<tbody>
<tr>
<td>U266 myeloma</td>
<td>P19 FR1 IGLV1</td>
<td></td>
<td>5</td>
<td>TQPPSTSET</td>
<td>9</td>
<td>0.76</td>
<td>0.40</td>
<td>1/90</td>
</tr>
<tr>
<td></td>
<td>P20 FR2 IGLV1</td>
<td></td>
<td>39</td>
<td>HLPGKAPKL</td>
<td>9</td>
<td>0.73</td>
<td>0.26</td>
<td>0/90</td>
</tr>
<tr>
<td></td>
<td>P21 FR3 IGLV1</td>
<td></td>
<td>71</td>
<td>SASLAISGL</td>
<td>9</td>
<td>0.68</td>
<td>0.15</td>
<td>12/90</td>
</tr>
<tr>
<td></td>
<td>P23 CDR1 IGLV1</td>
<td></td>
<td>26</td>
<td>TSNIGSNV</td>
<td>9</td>
<td>0.45</td>
<td>0.24</td>
<td>0/90</td>
</tr>
<tr>
<td></td>
<td>P25 CDR1 IGLV1</td>
<td></td>
<td>32</td>
<td>NSVNWYOH</td>
<td>9</td>
<td>0.21</td>
<td>1.29</td>
<td>1/90</td>
</tr>
<tr>
<td></td>
<td>P26 CDR3 IGLV1</td>
<td></td>
<td>90</td>
<td>ASWDRLNGL</td>
<td>10</td>
<td>10.92</td>
<td>0.26</td>
<td>0/90</td>
</tr>
<tr>
<td></td>
<td>P27 CDR1 IGLV1</td>
<td></td>
<td>9</td>
<td>STSETPGQV</td>
<td>10</td>
<td>3.96</td>
<td>0.53</td>
<td>0/90</td>
</tr>
<tr>
<td></td>
<td>P28 FR1 IGLV1</td>
<td></td>
<td>17</td>
<td>GVTISCSTS</td>
<td>10</td>
<td>0.09</td>
<td>0.15</td>
<td>0/90</td>
</tr>
<tr>
<td></td>
<td>P29 FR1 IGLV1</td>
<td></td>
<td>11</td>
<td>SETPGQGVT</td>
<td>10</td>
<td>0.20</td>
<td>0.45</td>
<td>0/90</td>
</tr>
<tr>
<td>Human CLL1</td>
<td>L50 FR1 IGLV2</td>
<td></td>
<td>29</td>
<td>SSVSGPSQ</td>
<td>10</td>
<td>0.91</td>
<td>0.07</td>
<td>7/90</td>
</tr>
<tr>
<td>Human FL1</td>
<td>L53 FR1 IGLV1</td>
<td></td>
<td>28</td>
<td>SABATPGQRV</td>
<td>10</td>
<td>0.96</td>
<td>0.06</td>
<td>2/90</td>
</tr>
<tr>
<td>Human FL2</td>
<td>L54 FR1 IGLV4</td>
<td></td>
<td>29</td>
<td>SASASLGAV</td>
<td>10</td>
<td>0.96</td>
<td>0.06</td>
<td>2/90</td>
</tr>
<tr>
<td>Human FL3</td>
<td>L61 FR1 IGLV1</td>
<td></td>
<td>16</td>
<td>KVTISCSG</td>
<td>10</td>
<td>0.28</td>
<td>0.06</td>
<td>2/90</td>
</tr>
<tr>
<td>Human PL1</td>
<td>K18 CDR2 IKGV5</td>
<td></td>
<td>50</td>
<td>LIYGTSPRA</td>
<td>9</td>
<td>3.7</td>
<td>0.52</td>
<td>1/123</td>
</tr>
</tbody>
</table>

Abbreviation: CDR, complementarity determining region.

b Soma tically mutated amino acids are given in bold.
c Estimate of half-time of disassociation and calculated score in arbitrary units.
d Mean fluorescence index = (mean fluorescence with peptide − mean fluorescence without peptide)/(mean fluorescence without peptide).

Individual peptide sequences were compared with Ig V region sequences available from either 90 FL patients with λ or 123 patients with κ light chain isotype, respectively.

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Candidate \( V_L \) epitopes shared by human FL

A current limitation of Id vaccines is the requirement for individualized manufacture, which could be partially overcome by identification of universal T-cell epitopes shared by multiple patients. To determine whether the immunogenic U266 and primary tumor \( V_L \) peptides were shared by other human B-cell tumors, we compared them to 90 \( \lambda \) and 123 \( \kappa \) light chain sequences from a panel of FL tumors (D. Gold, unpublished data). Interestingly, we observed that 12 FL tumors shared the P21 sequence whereas 1 FL each shared P19 and P25 epitopes. Seven FLs shared the L50 epitope, 2 FLs each shared the L53, L54, and L61 epitopes, and K18 and L10 epitopes were shared by one other primary FL each (Table 1). The two 2 most frequently shared peptides (P21 and L50) localized to the framework regions of VL and consisted of germ line sequences without somatic mutation. Overall, 27 of 90 (30%) FL tumors expressing \( \lambda \) light chain shared at least 1 of 13 epitopes we identified here.

To determine whether CTLs generated against a U266 peptide could lyse primary tumor cells expressing a shared epitope, we incubated donor-derived, P21-specific CTLs with HLA-A*0201 FL that expressed the P21 epitope (FL4, HLA-A2*/P21\(^\star\)). We observed significant lysis of FL target cells, but not PBMCs, from this patient or FL that did not express P21 (FL5, HLA-A2*/P21\(^\star\)), suggesting specificity for Id (Fig. 4C).
Discussion

Increasing data suggest that human T-cell immunity plays an important role in antitumor effects induced by Id vaccination with whole protein (17–19). Studies have identified T-cell epitopes harbored by Ig VH of human and Ig VL of murine B-cell tumors (20–29), but whether human Id VL harbor important T cell epitope remains unclear (25, 26). Two previous publications reported that Ig light chains contained few T-cell epitopes. In Dabadghao’s study, PBMCs from 5 myeloma patients were incubated with fragment F(ab)2, Fab, HC (heavy chain), or LC (light chain) of autologous Id protein to determine Id-specific T-cell proliferation. They found

Table 2. Immunogenicity of Id VL peptides derived from human U266 myeloma cell line and primary B-cell tumors

<table>
<thead>
<tr>
<th>Peptides</th>
<th>Peptide-specific IFN-γ (pg/mL) secretion&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ND1</td>
</tr>
<tr>
<td>P19</td>
<td>1,431.9</td>
</tr>
<tr>
<td>P20</td>
<td>1,203.9</td>
</tr>
<tr>
<td>P21</td>
<td>710.2</td>
</tr>
<tr>
<td>P23</td>
<td>1,817.3</td>
</tr>
<tr>
<td>P25</td>
<td>1,091.1</td>
</tr>
<tr>
<td>P26</td>
<td>716.0</td>
</tr>
<tr>
<td>P27</td>
<td>1,931.2</td>
</tr>
<tr>
<td>P28</td>
<td>2,126.6</td>
</tr>
<tr>
<td>P29</td>
<td>1,527.9</td>
</tr>
<tr>
<td>L50</td>
<td>0.0</td>
</tr>
<tr>
<td>L53</td>
<td>0.0</td>
</tr>
<tr>
<td>L54</td>
<td>0.0</td>
</tr>
<tr>
<td>L61</td>
<td>0.0</td>
</tr>
<tr>
<td>K18</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Abbreviation: ND, normal donor.

<sup>a</sup>Peptide-specific IFN-γ secretion = IFN-γ from T cells stimulated with Id VL peptide-pulsed T2 cells – IFN-γ from T cells stimulated with control peptide (HIV-Gag<sub>77-85</sub>)-pulsed T2 cells.

<sup>b</sup>No peptide-specific IFN-γ secretion detected.

Figure 2. The cytotoxic function of VL peptide–specific CTLs against id peptide or control HIV peptide-pulsed T2 cells. A, the cytotoxic function of U266-derived VL peptide–specific CTLs was tested against T2 cells pulsed with U266 or control HIV peptide. B, the cytotoxic function of donor CTL raised against primary B-cell tumor-derived VL peptides was tested against T2 cells pulsed with the respective human tumor–derived or control HIV peptide. Results are representative of 3 independent experiments.
that Ig fragments of F(ab)2, Fab, and HC can stimulate PBMC proliferation. However, none of the patients’ PBMCs proliferated to LC of Ig protein (25). In the study by Fagerberg and colleagues, peptides corresponding to the heavy chain and light chain of 1 myeloma Ig protein were synthesized and incubated with 1 myeloma patient’s PBMCs. Using ELISPOT assay, they found that only peptides derived from HC but none from LC of Ig protein could stimulate T cells to secrete IFN-γ (26). In our study, we have identified 14 peptides from Ig light chain.
chain (\(V_L\)) of U266 and primary B-cell tumors that can be used to generate 68 CTLs lines in vitro. These \(V_L\) CTLs lysed the peptide-pulsed T2 cell as well as tumor cells, indicating that \(V_L\) immunogenic epitopes are processed and presented by tumor cells. The differences between our results and previous studies may have resulted from several reasons. First, the patient’s PBMCs are not ideal to study protective T-cell immunity, as the immune balance is skewed toward immunosuppression (30). Second, the whole Id protein may harbor immune regulatory as well as stimulatory sequences, thus the identification of immunogenic epitope may be hampered by regulatory epitopes on the whole Id protein (31). Finally, significantly more peptides from patients were synthesized and tested in our study. Overall, our study suggests that immunogenic epitopes are present in \(V_L\) complementarity-determining regions and framework regions and are processed and presented by primary tumor cells and supports strategies for targeting \(V_L\) epitopes on B-cell tumors. CTLs targeting Id \(V_L\) may also have specific clinical usage against L chain-only secreting plasma cell dyscrasias (27).

Id vaccination significantly extended the disease-free survival of FL patients as shown in a recent controlled phase III trial, consistent with suggestions from prior pilot clinical trials (6, 32). The ability to prime HLA-A2\(^+\) donor CD8\(^+\) T cells against \(V_L\) epitopes may provide a strategy for improving adoptive therapy against B-cell malignancies. Previous work in human SCT, showing that the transfer of humoral, and to a lesser extent cellular, antigen-specific immunity to clinically important viral antigens from immune donors to recipients can occur, provides a rationale for transferring tumor antigen-specific immunity induced in donors (33–35). Vaccination of HLA-matched sibling donors with myeloma Id protein, with subsequent transfer of Id-specific immunity by SCT, has been shown to be feasible in a limited number of patients with myeloma (10, 11). Six donors were vaccinated with Id proteins (conjugated to KLH) isolated from the plasma of the myeloma patients prior to marrow harvest, and respective recipients were administered booster Id immunizations following transplantation. The vaccine was well tolerated by all donors and recipients. With median follow-up of 8 years, no long-term toxicity has been observed in any immunized donor. Vaccination induced specific cellular and/or humoral immune responses against Id and the vaccine carrier KLH in all donors. Two patients died within 30 days of SCT because of transplant-related complications, but Id-specific and KLH-specific T-cell responses were detected in all 4 remaining patients post- but not pre-bone marrow transplantation. All 4 surviving patients converted from partial to complete responses following SCT. Taken together, these preliminary results suggest that (i) Id protein can elicit a specific immune response in a healthy donor, (ii) direct transfer of Id-specific T-cell immunity can occur from donor to recipient, and (iii) donor-derived T-cell responses may not be blocked by circulating Id protein present in the patients during and after SCT, or by iatrogenic immunosuppression for GVHD prophylaxis. Our current data suggest that as an alternative to donor vaccination, immunogenic peptides may be used to selectively expand Id-specific T cells ex vivo to generate “educated” DLIs. Such primed T cells might enhance tumor specificity and limit GVHD complications of current DLI strategies.

Using a recently described method (14), we completed multiple T-cell stimulations within 2 weeks, such that the T cells are not exhausted at that time. Instead, these T cells are at much younger stage than T cells traditionally stimulated 3 to 4 times weekly. Even after these multiple stimulations, we observed that the T cells retained effector function and were able to lyse peptide-pulsed and tumor cell targets (Figs. 2 and 3). Furthermore, as described, using an established rapid expansion protocol, we showed feasibility of expanding such Id-specific T cells in large numbers. We are thus now in a position to conduct future in vivo experiments to determine whether adoptively transferred T cells recognizing shared epitopes would persist and be active.

Finally, although outside of the scope of the current study, one of the important questions in human tumor immunology is to determine whether autologous tumor-specific CTLs preexist in patients. In light of the immunogenicity of Id light chain peptides found in this study, specifically, it will be important to determine whether Ig light chain-specific CTLs preexist in the blood of patients with B-cell tumors and whether such precursors can be expanded by vaccination or adoptive transfer. Previous studies have suggested the existence and function of such tumor-specific T cells in B-cell tumor patients (36, 37). Experiments testing the ability of human tumor \(V_L\) peptides to generate autologous Id-specific T cells are under active investigation in our laboratory.

Disclosure of Potential Conflicts of Interest

L.W. Kwak received commercial research grant from Celgene, has ownership interest in XEME BioPharma, Inc., and is a consultant/advisory board member of Biovest International, Inc., and Antigenics Inc.

Authors’ Contributions

J. Weng and L.W. Kwak designed experiments; J. Weng, S.-C. Cha, and M.S. Popescu carried out experiments; S. Matsueda, G. Alatrash, J.J. Moll- dreem, Q. Yi, M. Wang, and S.S. Neelapu provided critical reagents or suggestions; and J. Weng, S.S. Neelapu, and L.W. Kwak analyzed data and wrote the manuscript.

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