Myeloma Bone Marrow Plasma Cells: Evidence for Their Capacity as Antigen-Presenting Cells

By Qing Yi, Sunil Dabadghao, Anders Östergård, Susanne Bergenbrant, and Göran Holm

Myeloma plasma cells constitute 10% to 90% of the total bone marrow cell count in patients with multiple myeloma (MM). These cells express a variety of cell surface markers, such as HLA-ABC and HLA-DR, and surface antigens that are necessary for professional antigen-presenting cells, including adhesion and costimulatory molecules. In this study, we examined the expression of major histocompatibility complex (MHC) and costimulatory molecules on CD38\(^{\text{bright}}\) plasma cells in bone marrow aspirates from eight MM patients. Small percentages of plasma cells expressed weak but detectable levels of HLA-DRA, HLA-DRB, CD40, CD80, and CD86, which could be upregulated by interferon-\(\gamma\) (IFN-\(\gamma\)) and tumor necrosis factor-\(\alpha\). CD38\(^{++}\) plasma cell and CD38\(^{\text{dim,-}}\) cells were sorted from freshly isolated bone marrow mononuclear cells and tested for their capacity to act as antigen-presenting cells. Indeed, both CD38\(^{++}\) plasma cells and CD38\(^{+}\) cells were able to stimulate allogeneic T cells and present the soluble antigens purified protein derivative and tetanus toxoid to autologous T cells. Recognition of the antigens led to T-cell proliferation and secretion of IFN-\(\gamma\) and was MHC class-I and -II restricted. Antigen processing and presentation by CD38\(^{++}\) and CD38\(^{+}\) cells were abolished by treatment of the cells with chloroquine. Hence, our study provides for the first time evidence that myeloma plasma cells may act as antigen-presenting cells. Further studies are warranted to examine in detail the molecules required for inducing T-cell stimulation.

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Multiple Myeloma (MM) is a B-cell neoplasia characterized by clonal expansion of malignant plasma cells in the bone marrow. These plasma cells produce a monoclonal Ig that can be detected in the serum and/or urine. Plasma cells represent the terminal differentiation stage of B-cell development. In MM, plasma cells constitute at least 10% and can even reach greater than 90% of the total bone marrow cell count. The growth and differentiation of myeloma plasma cells are believed to be regulated by a functional interplay between the tumor cells and the bone marrow microenvironment mediated by cytokines such as interleukin-6 (IL-6) and by close cellular contact between myeloma cells and marrow stromal components (reviewed in Moscinski and Ballester and Klein et al).

The immune system has a potential role in the regulation of MM. One important aspect is whether the bone marrow myeloma plasma cells can be recognized and regulated by tumor-specific T cells. Myeloma plasma cells may express a variety of cell surface markers, such as CD10, CD33, and HLA-DR. In addition, adhesion molecules such as CD44, CD56, CD54, and VLA-4 and signaling or costimulatory molecules CD40, CD28, and CD80 were found on freshly isolated myeloma bone marrow plasma cells or myeloma-derived cell lines. Thus, based on the expression of the surface antigens, myeloma plasma cells may belong to the category of antigen-presenting cells.

Materials and Methods

Cell Preparation. Bone marrow aspirates were obtained from eight patients with MM (Table 1). BMMCs were isolated by Ficoll-Paque (Pharmacia, Uppsala, Sweden) density gradient centrifugation. The cells were washed twice and resuspended in culture medium (RPMI 1640) supplemented with L-glutamine (4 mmol/L), penicillin (100 IU/mL), streptomycin (100 \(\mu\)g/mL), and 10% heat-inactivated pooled serum from individuals with blood group AB Rh.

PBMCs were isolated from heparinized blood by Ficoll-Paque (Pharmacia) density gradient centrifugation and suspended in medium as described above. T cells were isolated from PBMCs incubated on a Petri dish for 30 minutes (to obtain adherent cells) and the remaining monocytes were depleted using iron powder. The resulting cell population was incubated with anti-CD19 antibody-coated Dynabeads (M-450; Dynal A.S., Oslo, Norway) at a bead to target cell ratio of 50:1 to deplete B cells. CD3 T cells in the monocyte-depleted and B-cell-depleted population were greater than 95%. CD14 monocytes in adherent cells were greater than 60%.

Monoclonal antibodies (MoAbs) and flow cytometry analysis. For the identification of bone marrow plasma cells and their surface antigens, the following MoAbs were used: phycoerythrin (PE)-conjugated anti-CD38 (Leu-17; Becton Dickinson Immunocytometry...
Table 1. Patients’ Characteristics and Percentage of CD38⁺⁺ Plasma Cells Expressing Surface MHC (HLA), Signaling or Costimulatory Molecules, and CD19 Antigen

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)/Sex</th>
<th>Clinical Stage</th>
<th>Monoclonal Ig</th>
<th>% of CD38⁺⁺ Plasma Cells Expressing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72/F</td>
<td>IIA</td>
<td>IgG1α</td>
<td>DR  11.6</td>
</tr>
<tr>
<td>2</td>
<td>72/F</td>
<td>IA</td>
<td>IgG1κ</td>
<td>44.0</td>
</tr>
<tr>
<td>3</td>
<td>70/M</td>
<td>IIIB</td>
<td>IgG1κ</td>
<td>13.4</td>
</tr>
<tr>
<td>4</td>
<td>55/M</td>
<td>IA</td>
<td>IgG1κ</td>
<td>10.0</td>
</tr>
<tr>
<td>5</td>
<td>67/M</td>
<td>IIA</td>
<td>IgAκ</td>
<td>33.2</td>
</tr>
<tr>
<td>6</td>
<td>60/M</td>
<td>IIA</td>
<td>IgG1κ</td>
<td>12.6</td>
</tr>
<tr>
<td>7</td>
<td>89/F</td>
<td>IA</td>
<td>IgG1κ</td>
<td>22.7</td>
</tr>
<tr>
<td>8</td>
<td>66/M</td>
<td>IA</td>
<td>IgAκ</td>
<td>9.2</td>
</tr>
<tr>
<td>Median</td>
<td>69/—</td>
<td>—</td>
<td>—</td>
<td>12.5</td>
</tr>
</tbody>
</table>

Abbreviations: PC, plasma cells; BM, bone marrow; ND, not done.

Systems, Mountain View, CA) and fluorescein isothiocyanate-conjugated anti–HLA-DR, anti–HLA–DQ (Becton Dickinson), HLA-ABC (Chemicon International Inc, Temecula, CA), CD80 (MAB104; Immunotech, Marseille, France), CD86 (2331; Pharmingen, San Diego, CA), CD40 (5C3; Pharmingen), and CD19 (Becton Dickinson). BMMCs were stained with these antibodies and analyzed by a FACScan flow cytometer (Becton Dickinson). CD38⁺⁺ plasma cells expressing the antigens were determined.

**Bone marrow cell culture.** For the study of inducible surface antigens on plasma cells, BMMCs were cultured in the absence or presence of 500 U/mL interferon-γ (IFN-γ), 500 U/mL tumor necrosis factor-α (TNF-α), or 10 ng/mL IL-6 (Genzyme Corp, Boston, MA) for 48 hours. After culture, cells were harvested, washed, and analyzed by FACScan for the expression of surface MHC class I and II molecules as well as CD80, CD86, and CD40 antigens on CD38⁺⁺ plasma cells. Both the percentage of CD38⁺⁺ plasma cells expressing the antigens and the level of expression of the antigen defined as mean fluorescence intensity (MFI) were determined.

**Fluorescence-activated cell sorting (FACS) sorting of BMMCs into CD38⁺⁺ and CD38⁺ populations.** Cell sorting was performed with BMMCs from seven patients with MM. A total number of 20 to 30 x 10⁶ BMMCs were stained with PE-conjugated anti–CD38 antibody at 4°C for 30 minutes. After staining, cells were washed twice and resuspended in 4 mL of phosphate-buffered saline. Sorting was performed on a FACScan Vantage flow cytometer (Becton Dickinson). Cells were collected into tubes containing 1 mL of complete cell culture medium and 5 to 8 x 10⁵ cells were collected into each tube. The cells were sorted into two fractions containing either CD38⁺⁺ or CD38⁺ cells, resuspended in complete cell culture medium, and used for functional studies. Contamination of CD14⁺ monocytes and CD20⁺ B cells in the CD38⁺⁺ population was undetectable (<0.1%).

![](image1.png)

**Fig 1.** Sorting of CD38⁺⁺ and CD38⁺ cells from BMMCs of an MM patient. BMMCs were stained with PE-conjugated CD38 MoAb and sorting was performed with a FACS Vantage flow cytometer.
Table 2. Expression of MHC Class-I and -II and Signaling or Costimulatory Molecules on Noninduced and Cytokine-Induced Bone Marrow CD38++ Plasma Cells

<table>
<thead>
<tr>
<th>MFI</th>
<th>MFI</th>
<th>Ratio*</th>
<th>MFI</th>
<th>Ratio*</th>
<th>MFI</th>
<th>Ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-DR</td>
<td>497 (417-518)</td>
<td>1,019 (686-1,615)</td>
<td>2.1</td>
<td>840 (320-1,219)</td>
<td>1.7</td>
<td>540 (440-640)</td>
</tr>
<tr>
<td>HLA-DQ</td>
<td>300 (270-340)</td>
<td>716 (560-890)</td>
<td>2.4</td>
<td>490 (402-550)</td>
<td>1.6</td>
<td>334 (302-390)</td>
</tr>
<tr>
<td>HLA-ABC</td>
<td>1,444 (1,217-2,124)</td>
<td>3,719 (2,535-4,835)</td>
<td>2.6</td>
<td>2,998 (1,332-5,001)</td>
<td>2.1</td>
<td>2,077 (1,211-2,944)</td>
</tr>
<tr>
<td>CD40</td>
<td>175 (146-165)</td>
<td>278 (125-280)</td>
<td>1.6</td>
<td>176 (120-227)</td>
<td>1.1</td>
<td>141 (112-172)</td>
</tr>
<tr>
<td>CD80</td>
<td>135 (107-163)</td>
<td>286 (114-286)</td>
<td>2.1</td>
<td>273 (92-437)</td>
<td>2.0</td>
<td>142 (112-172)</td>
</tr>
<tr>
<td>CD86</td>
<td>180 (156-209)</td>
<td>393 (226-407)</td>
<td>2.2</td>
<td>246 (198-279)</td>
<td>1.4</td>
<td>257 (229-285)</td>
</tr>
</tbody>
</table>

Median and range (in parentheses) of MFI are shown. Data were obtained from experiments using BMMCs from four different MM patients.

* Ratio was calculated from the median value of MFI from cytokine-induced cells divided by the median of MFI from noninduced cells.

Cytoplasmic light chain staining. A total number of 1 × 10^6 cells from each sorted population was cytocentrifuged for 5 minutes at 450 rpm on slides and fixed with 70% acetone at −20°C for 10 minutes. After fixation, slides were washed in phosphate-buffered saline, incubated for 30 minutes with alkaline phosphatase-conjugated rabbit anti-α or anti-λ MoAb (Sigma, St Louis, MO), and stained with substrate (fast red; Vector Laboratories, Sigma) was used to inhibit antigen processing and presentation. 23

RESULTS

To test if sorted plasma cells were able to present the soluble antigens PPD and TT, 1 × 10^5 T cells were cultured with different numbers of autologous adherent cells (monocytes) or irradiated CD38++ and CD38−, unfractionated BMMCs or PBMCs were irradiated with 30 Gy from a 137Cs source and added in graded doses as stimulators for 1 × 10^6 allogeneic adult PBMC in 96-well round-bottomed microtitre plates (Nunc U96; Nunclon, Roskilde, Denmark). Proliferation was determined on day 6 with the addition of 1 μCi/well of ³H-thymidine (Amersham Life Science, Aylesbury, UK) 18 hours before harvest. The results are expressed as the mean counts per minute (cpm) of triplicate values.

Antigen-presentation assay. To test if sorted plasma cells were able to present the soluble antigens PPD and TT, 1 × 10^5 T cells were cultured with different numbers of autologous adherent cells (monocytes) or irradiated CD38++, CD38−, and BMMCs in the absence or presence of PPD (2.5 μg/mL) or TT (50 ng/mL). Antigen-induced T-cell stimulation was determined on day 3 by ³H-thymidine incorporation assay and was determined on day 2 by enumerating the number of IFN-γ-secreting cells using an enzyme-linked immunospot (ELISPOT) assay. 21,22 The results are expressed as total number of IFN-γ-secreting cells/10^5 T cells.

MHC restriction. To study MHC molecules involved in allogeneic MLR and autologous antigen presentation, mouse MoAb against HLA-DR (IgG2b; Immunotech), HLA-ABC (IgG2b; Chemicon), and a mouse isotypic control IgG2b (Immunotech) were used. The MoAb or control IgG was added to cell cultures at a final concentration of 1 μg/mL, for the whole incubation period.21 Results are expressed as the percentage of inhibition compared with cultures without the addition of anti-MHC MoAb or control IgG.

Chloroquine treatment. A lysosomotropic agent (chloroquine; Sigma) was used to inhibit antigen processing and presentation. 23

The effect of the drug was evaluated by adding it, at a final concentration of 50 μmol/L, to cultures containing 1 × 10^5 CD38++ or CD38− cells and 1 × 10^6 purified autologous T cells with the addition of PPD or concanavalin A (Con A; 20 μg/mL). Alternatively, CD38++ or CD38− cells were incubated with or without PPD in the absence or presence of chloroquine (200 μmol/L) for 4 hours at 37°C and then used as antigen-presenting cells.

RESULTS

Morphology and cytoplasmic light chain of CD38++ and CD38− cells. BMMCs from MM patients were sorted into CD38++ and CD38− cells (Fig 1). Staining with May-Grünewald-Giemsa showed that 99% of CD38++ cells had plasma cell cytology, whereas CD38− population contained plasma cells (~10%), lymphocytes, plasmablasts, and other types of bone marrow cells. Because cytoplasmic Ig is a typical feature of plasma cells, staining of the sorted cells with antibodies against human light chains was performed on slides. CD38++ plasma and 10% of CD38− cells were stained with antibody against the same light chain as the individual patient’s monoclonal Ig (data not shown).
Phenotype of CD38++ plasma cells. A gate on CD38++ plasma cells was set and used to analyze their expression of other surface molecules. The percentages of bone marrow CD38++ plasma cells expressing MHC and costimulatory molecules varied between patients (Table 1). CD19+ plasma cells were very few, which is in accord with previous observation.7,24

Modulation of surface antigens by IFN-γ, TNF-α, and IL-6. BMMCs from four MM patients were cultured for 48 hours with or without the addition of IFN-γ, TNF-α, or IL-6. Noninduced bone marrow CD38++ plasma cells express high level of HLA-ABC, and a small percentage of the plasma cells expressed low but detectable level of HLA-DR and HLA-DQ and signaling or costimulatory antigens CD40, CD80, and CD86 (Table 2). After culture with IFN-γ for 48 hours, a greater than twofold increase in MFI of all the antigens, except CD40 (1.6-fold), was noted on CD38++ plasma cells. TNF-α, to a lesser extent, had similar effects (1.4- to 2.1-fold enhancement). The expression of HLA-ABC and CD86, but not other antigens, was slightly upregulated by IL-6 (Table 2).

Coculture of BMMCs with cytokines also increased the percentage of CD38++ plasma cells expressing MHC and costimulatory molecules (Fig 2). Among the cytokines, IFN-γ was most effective: it induced an increased population of CD38++ plasma cells expressing HLA-DR (11.6% to 22.6%; 2.0-fold increase), HLA-DQ (11.8% to 18.7%; 1.6-fold), CD40 (8% to 28.6%; 3.6-fold), CD80 (5.1% to 13.3%; 2.6-fold), and CD86 (9.8% to 19.0%; 1.9-fold). TNF-α also had similar effects and induced 1.5- to 2.4-fold increases in cells expressing HLA-DR or costimulatory molecules. IL-6 induced a 2.8-fold increase in CD80+CD38++ plasma cells but had no effect on other cell populations (Fig 2).

Stimulatory capacity of CD38++ plasma cells and CD38−cells (MLR). Sorted CD38++ plasma cells and CD38−cells were compared with BMMCs and PBMCs for their capacity to stimulate alloreactive T cells. Different numbers of plasma cells, BMMCs, or PBMCs from the same patient were cultured with 1 × 10⁵ of allogeneic PBMCs. As exemplified by the experiments in Fig 3, a dose-dependent response curve was obtained. A total of 1 × 10⁵ CD38++ plasma cells, CD38−cells, and BMMCs and 0.5 × 10⁵ PBMCs induced a maximal response. Cultures with stimulatory cells or allogeneic PBMCs alone had a very low background count (data not shown). It is interesting to note that CD38+++ plasma cells induced a stronger response than other cells (Fig 3 and Table 3). Similar results were reproduced with cells from the other four MM patients. The results obtained with the optimal number of stimulatory cells (10⁵ CD38+++ plasma cells, CD38−cells, and BMMCs and 0.5 × 10⁵ PBMCs) and control experiments from a total of five patients are summarized and shown in Table 3.

Presentation of the soluble antigens PPD and TT to autologous T cells. To evaluate the capacity of sorted plasma cells to present the soluble antigens PPD and TT, we compared CD38+++ plasma cells, CD38−cells, BMMCs, and monocytes (adherent cells) for their capacity to present the

Table 3. Induction of T-Cell Stimulation by Bone Marrow CD38+++ Plasma Cells, CD38−Cells, and Antigen-Presenting Cells

<table>
<thead>
<tr>
<th>APC</th>
<th>MLR (cpm)</th>
<th>Ag-Induced Cell Proliferation (cpm)</th>
<th>No. of Ag-Induced IFN-γ−Secreting Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Ag</td>
<td>PPD</td>
<td>TT</td>
</tr>
<tr>
<td>CD38++</td>
<td>462 (304-786)</td>
<td>14,753 (4,370-35,670)</td>
<td>396 (313-554)</td>
</tr>
<tr>
<td>CD38−</td>
<td>459 (242-870)</td>
<td>10,451 (7,511-34,307)</td>
<td>477 (367-898)</td>
</tr>
<tr>
<td>BMMCs</td>
<td>542 (260-623)</td>
<td>11,600 (6,344-40,151)</td>
<td>504 (359-980)</td>
</tr>
<tr>
<td>PBMCs</td>
<td>482 (170-526)</td>
<td>11,989 (7,001-31,474)</td>
<td>ND</td>
</tr>
<tr>
<td>Me</td>
<td>ND</td>
<td>ND</td>
<td>418 (376-772)</td>
</tr>
<tr>
<td>No APCs</td>
<td>422 (302-1,373)</td>
<td>537 (283-950)</td>
<td>659 (560-660)</td>
</tr>
</tbody>
</table>

Median and range (in parentheses) are shown. The results were obtained from experiments using an optimal amount of antigen-presenting cells from five MM patients.

Abbreviations: Ag, antigen; APCs, antigen-presenting cells; AlloPBMCs, allogeneic PBMCs; ND, not done; Me, monocytes.

* Data obtained from cultures with allogeneic PBMCs only.
† Data obtained from cultures with purified T cells only.
cells, CD38⁺ cells, or BMMCs were not yet sufficient to induce the maximal response (Fig 4A). This is also true when soluble antigen TT was used (data not shown). Similar results also were obtained by enumerating antigen-induced IFN-γ-secreting cells (Fig 4B). The T-cell stimulation was clearly antigen-dependent, because coculture of T cells with sorted plasma cells, BMMCs, or monocytes without the antigens yielded the same low counts (cpm or number of IFN-γ-secreting cells) as cultures with antigen-presenting cells or T cells alone (data not shown). We have repeated these experiments with sorted cells from the other four MM patients, and the results were reproducible. Table 3 shows the summarized data from the five patients obtained with the optimal number of antigen-presenting cells (1 × 10⁵ CD38⁺⁺, CD38⁺, and BMMCs and 1 × 10⁴ monocytes) and control experiments.

MHC restriction in MLR and antigen presentation by the plasma cells. Mouse MoAb against human MHC class I (HLA-ABC) or class II (HLA-DR) were used to inhibit alloreactive MLR and PPD-induced T-cell stimulation. Although both MoAb showed inhibitory effects, MoAb against HLA-ABC resulted in a higher percentage of inhibition than MoAb against HLA-DR on CD38⁺⁺ and CD38⁺ cell-induced alloreactive (MLR; Fig 5A) and autologous T-cell stimulation (PPD-induced; Fig 5B). When BMMCs and, especially, monocytes were used as the antigen-presenting cells, PPD-induced T-cell stimulation was inhibited predominantly by anti-HLA-DR antibody (75% and 85%, respectively), which is consistent with our previous observation. The unspecific inhibition by mouse isotypic control IgG was 4% to 10%.

Effect of chloroquine. PPD-induced T-cell stimulation was totally abolished by the presence of chloroquine in the culture (Table 4), whereas cell activation induced by Con A was not affected (data not shown). An inhibitory effect was also observed when the drug was present during the pulse of CD38⁺⁺ with PPD or when chloroquine-pretreated cells were used as antigen-presenting cells (Table 4). Similar results were obtained with CD38⁺⁺ cells (data not shown).

DISCUSSION

This study describes the capacity of freshly isolated bone marrow plasma cells from patients with MM to act as antigen-presenting cells. First, we analyzed the MHC (HLA-DR, HLA-DQ, and HLA-ABC) and signaling or costimulatory molecules (CD40, CD80, and CD86) on CD38⁺⁺ plasma cells and found that these molecules could be upregulated by cytokines such as IFN-γ and TNF-α. Second, we showed that sorted CD38⁺⁺ plasma cells and CD38⁺⁺ cells were able to induce a strong allogeneic T-cell stimulation and to present PPD and TT to autologous T cells. Thus, our study provides evidence that myeloma plasma cells can act as fully functional antigen-presenting cells in vitro. Whether the cytokine-induced upregulation of the expression of the molecules on plasma cells may affect their capacity to stimulate alloreactive T cells and present antigens to T cells is currently under investigation.

Generally, stimulated macrophages, activated B cells, and dendritic cells are the professional antigen-presenting cells. They are required for the initiation of antigen-specific reac-
Fig 5. MHC restriction in allogeneic MLR (A) and PPD-induced T-cell stimulation (B) using CD38" plasma cells, CD38" cells, BMMCs, and monocytes as antigen-presenting cells. The percentage (mean ± SD of 3 experiments) of inhibition induced by MoAb against HLA-DR (■), HLA-ABC (□), and a mouse control IgG (△) is shown.

Table 4. Effect of Chloroquine on Antigen Processing and Presentation by CD38\(^*\) Plasma Cells

<table>
<thead>
<tr>
<th>Experiments</th>
<th>Chloroquine</th>
<th>No Antigen</th>
<th>PPD</th>
<th>Inhibition (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence in cultures</td>
<td>–</td>
<td>320 ± 110</td>
<td>2,320 ± 430</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>298 ± 122</td>
<td>302 ± 116</td>
<td>100</td>
</tr>
<tr>
<td>During pulse of plasma cells with PPD</td>
<td>–</td>
<td>240 ± 88</td>
<td>1,504 ± 340</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>280 ± 110</td>
<td>380 ± 122</td>
<td>92</td>
</tr>
<tr>
<td>Pretreatment of plasma cells</td>
<td>–</td>
<td>250 ± 98</td>
<td>1,882 ± 240</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>220 ± 112</td>
<td>579 ± 125</td>
<td>78</td>
</tr>
</tbody>
</table>

PPD-induced T-cell proliferation was measured on day 6. Means ± SD were determined on triplicate values of two experiments.
may also express costimulatory molecules. It is evident from these studies that most of the myeloma-derived cell lines were CD80+/12,13. A weak expression of CD80 was detected on freshly isolated myeloma plasma cells from 9% of MM patients,15 which is in line with our results. In addition, the present study also showed that 12% of CD38+/ CD86 plasma cells. Third, we have shown that the expression loss or downregulation of T-cell receptor z were CD80 AID Blood 0016 / 5h3c$$$301 07-31-97 21:58:55 blda WBS: Blood AID Blood 0016 / 5h3c$$$301 07-31-97 21:58:55 blda WBS: Blood such interaction and killing take place in vivo? If they do, son K: CD40 ligand triggered interleukin-6 secretion in multiple present on 12% of plasma cells, and both CD80 and CD86 7. Leo R, Boeker M, Peest D, Hein R, Bartl R, Gessner JE, reasonable that the plasma cells may be able to provide the cells is not conflicting with the ability of plasma cells to do so in the present study. On the other hand, CD86 was present on 12% of plasma cells, and both CD80 and CD86 expression could be upregulated by cytokines. Thus, it is also be involved in these T-cell responses. Nevertheless, studies suggest that the activation of naive T cells is critically independent on costimulatory signals, whereas memory T cells are less dependent on them for activation.26,32 Considering that the plasma cells stimulated allogeneic adult, not cord, T cells and presented antigens to antigen-primed or memory T cells (secondary responses), the low expression of CD80 on the cells is not conflicting with the ability of plasma cells to do so in the present study. On the other hand, CD86 was present on 12% of plasma cells, and both CD80 and CD86 expression could be upregulated by cytokines. Thus, it is reasonable that the plasma cells may be able to provide necessary costimulatory signals to the T cells.

This study indicates that myeloma plasma cells have the capacity to act as antigen-presenting cells and can thus be recognized by T cells in vitro. It also suggests that T cells, especially tumor-specific T cells, may play a role in regulation of the growth and differentiation of myeloma cells in vivo. Idiotypes present on the monoclonal Ig have been considered as the best defined tumor-specific antigen in MM. Thus, idiotypic-specific T cells that have been shown in the patients 20,22 are one, if not the only, type of tumor-specific T cells that may interact with the myeloma plasma cells. If idiotypic-specific T cells are of the CD8+ cytotoxic cells, as we have shown occasionally in some of MM patients, the interaction between them may lead to killing of such antigen-presenting cells.33-35 However, some questions remain. Does such interaction and killing take place in vivo? If they do, why is there still a large number of tumor cells in the pa-
tients? One of the possible explanations is that the tumor cells do not express sufficient costimulatory molecules on the surface and, as a result, are not able to prime antitumor immunity, especially the cytotoxic T-cell response. Instead, T-cell tolerance may be induced.26 The other possibilities may include that the function of T cells is deficient, such as loss or downregulation of T-cell receptor z chain that have been found in other tumor systems,27,28 as well as the presence of tumor-specific type-II T cells29 that may suppress the function of type-I cells by cytokines such as interleukin-10. Nevertheless, the understanding of the antigen-presentation capacity of myeloma plasma cells may help to develop tumor-specific immunotherapy in MM.

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