Human Monoclonal Antibodies Reactive with Human Myelomonocytic Leukemia Cells


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ABSTRACT

Peripheral blood mononuclear cells from a patient with chronic myelogenous leukemia (CML), in remission, were depleted of CD8-positive T-cells and cultured with Epstein-Barr virus. Four of 20 cultures (20%) secreted human IgG antibodies selectively reactive with the cell surfaces of certain human leukemia cell lines. Three polyclonal, Epstein-Barr virus-transformed, B-cell lines were expanded and fused with the human-mouse myeloma analogue HMMA2.11TG/O. Antibody from secreting clones HL 1.2 (IgG1), HL 2.1 (IgG3), and HL 3.1 (IgG2) have been characterized. All three react with HL-60 (promyelocytic), RWLeu4 (CML promyelocytic), and U937 (monocytic), but not with KG-1 (lymphoblastic) or K562 (CML erythroid). There is no reactivity with T-cell lines, Burkitt's cell lines, pre-B-leukemia cell lines, or an undifferentiated CML cell line, BV173. Leukemic cells from two of seven patients with acute myelogenous leukemia and one of five with acute lymphocytic leukemia react with all three antibodies. Normal lymphocytes, monocytes, polymorphonuclear cells, red blood cells, bone marrow cells, and platelets do not react. Samples from patients with other diverse hematopoietic malignancies showed no reactivity. Immunoprecipitations suggest that the reactive antigen(s) is a lactoperoxidase iodinatable series of cell surface proteins with molecular weights of 42,000-54,000 and a noniodinatable protein with a molecular weight of 82,000. Based on these data these monoclonal antibodies appear to react with myelomonocytic leukemic cells and may detect a leukemia-specific antigen or a highly restricted differentiation antigen.

INTRODUCTION

Autoantibody responses to autologous tumors have been noted in a variety of human malignancies. Of particular interest, serological studies of patients with diverse acute and chronic leukemias have demonstrated the presence of human antibodies on fresh leukemic cells. Reactivity of these antibodies was frequently found to extend to allogeneic leukemias but not normal cells (1-4). These studies suggest that tumor-specific antigens are present on the cell surfaces of human leukemic blasts and that the patient can recognize these antigens as foreign or abnormal. Such tumor-specific or tumor-related antigens may represent virally encoded antigens such as those seen with human T-cell leukemia virus I-associated lymphomas and leukemias, altered growth factor receptors, oncogenic antigens, or normal cellular antigens presented in an abnormal context.

The role of these antibodies and the antigens with which they react may be important in understanding the pathogenesis of these diseases and in developing therapeutic strategies. However, with the exception of human T-cell leukemia virus I antigens and antibodies, evaluation of these responses has not proceeded (5, 6). In part this may be due to the polyclonal nature of the human humoral response and the difficulty in performing reproducible studies with these polyclonal sera and heterogenous leukemias. It is apparent that to study these antibodies it would be important to obtain them in large quantities and pure form. Human monoclonal antibody technology can provide these reagents but until recently has not been available (7).

In the present study we describe the production and initial characterization of three human monoclonal antibodies obtained from a single patient with CML. These antibodies react with leukemic cells of myelomonocytic origin, recognizing antigenic determinants on the cell surfaces of several human myelomonocytic cell lines and leukemic blasts from patients with certain acute leukemias, but not with normal hematopoietic cells of diverse origin.

MATERIALS AND METHODS

Cell Culture. Cell lines and established hybridomas were grown in a minimum essential medium lacking nucleosides, supplemented with: 1 mM sodium pyruvate, 2 mM L-glutamine, 1% (v/v) nonessential amino acids, 10% (v/v) fetal bovine serum (high cloning efficiency and growth promotion; GIBCO, Grand Island, NY), 0.22% (w/v) sodium bicarbonate, and 50 μg/ml gentamicin. All other cell culture was performed with the same media containing 20% fetal bovine serum. Other additives were included as indicated. Cultures growing in flasks were flushed, sealed with a 5% CO2/air (v/v) mixture and maintained at 37°C. Repeated gassings with the CO2 were performed as needed to maintain proper pH. Cultures in microtiter plates or multilwell plates were incubated in a 5% CO2 atmosphere at 37°C in a humidified incubator.

Cell Lines. The HMMA2.11TG/O cell line, a nonsecreting human mouse myeloma analogue developed in this laboratory, was used for fusions (HB 9583, ATCC, Rockville, MD) (7). The B95-8 marmoset cell line was used as a source of EBV for cell transformation. The OKT8 hybridoma was obtained from the ATCC (CRL 8014, ATCC, Rockville, MD). The origins of the leukemic cell lines used in these studies are described in several reviews (8-10). These cell lines were kindly supplied by a number of investigators.4

Volunteer and Patient Cells. After informed consent, PBMC and bone marrow mononuclear cells were obtained by venipuncture or bone marrow aspiration in preservation-free heparin and separated from contaminating cells by density gradient separation as previously described (7). If not used immediately, cells were stored by cryopreservation in liquid nitrogen after resuspension in media containing 10% dimethyl sulfoxide.

Cell Fusion. Fusions were performed according to our standard procedure (7). In brief, the human-mouse myeloma analogue HMMA 2.11TG/O was fused in a minimum ratio of 2:1 with the other parental cells. Fused cells were distributed in 96-well microtiter plates

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2 To whom requests for reprints should be addressed, at Division of Oncology/Hematology, Roger Williams General Hospital, Brown University Medical School, 825 Chalkstone Avenue, Providence, RI 02908.

3 The abbreviations used are: CML, chronic myelogenous leukemia; EBV, Epstein-Barr virus; HAT, hypoxanthine, aminopterin, thymidine; HT, hypoxanthine, thymidine; HuNobo, human monoclonal antibody; SDS-PAGE, sodium dodecyl sulfate-polyacrylamide gel electrophoresis; ALL, acute lymphocytic leukemia; PBMC, peripheral blood mononuclear cells; PSC, Puck's saline G; PSC/WO, Puck's saline G without calcium and magnesium; PBS, phosphate buffered saline; PSC/S, Puck's saline G with 2.5% fetal bovine serum; RIPA, radioimmunoprecipitation assay.

4 Cell lines were kindly supplied by Dr. H. Lazarus (Centecor Corporation, Malvern, PA), Dr. R. Todd (University of Michigan, Ann Arbor, MI), Dr. J. Ritz (Dana Farber Cancer Institute, Boston, MA), Dr. J. Pesando (Biomembrane Institute, Seattle, WA), and Dr. M. Weimann (Roger Williams General Hospital, Providence, RI).

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in HAT-containing media. The number of cells seeded into each well in any experiment was based on the maximum number of potential hybrids given a hypothetical 1/1 fusion efficiency. The final volume in each well was 200 µl. In all experiments 10 µM ouabain in 50 µl of media with HT was added to yield a 2 µM ouabain concentration in each well 24 h after fusion to prevent the growth of uncloned transformed cells. A concentration of 2 µM ouabain was maintained in the wells for 1 week, after which routine feeding was performed. Fusions were fed at 4–7-day intervals by removal of 100–150 µl of media and replacement with an equal volume of media containing HT. After selection for expansion, cells were transferred to 24-well multwell plates in media containing HT and were maintained in HT until they were passed once in flasks. Hybridomas were cloned by resuspension and selection for expansion, cells were transferred to 24-well multiwell plates such that an average of 1 cell/100 µl/well was obtained. Cloned cells were fed at weekly intervals with media lacking HT.

Complement Depletion of Selected T-Cells and EBV Transformation. PBMs were selectively depleted of CD8-positive T-cells by antibody-mediated complement lysis. Cells were suspended at a density of 1 x 10^9/ml in media and 100 µl of culture supernatant from an OKT8 culture were added. The cells were incubated for 30 min at room temperature, rabbit complement (Pel Freeze, Brown Deer, WI) was added at a final concentration of 1:5, and the cells incubated for 1 h at 37°C. The cells were then washed three times with Puck’s saline G without calcium or magnesium.

For EBV transformation, PBMs were placed in 24-well plates such that 0.2–0.3 x 10^6 cells per well, in 1.0 ml of media containing a 1:10 dilution of stock B95-8 supernatant according to the prelysis cell number. EBV-transformed cultures were maintained by feeding weekly with the addition of small amounts of media until cell growth was observed and then every 3–4 days. Growing cultures were treated as above.

Indirect Immunofluorescence of Cell Surface Antigens. Indirect immunofluorescence for the detection of cell surface antigens was performed as previously described with some modifications (11). In brief, 1.0 x 10^6 live cells per sample were washed with PBS. To block Fc binding, cells were incubated with 100 µl of nonspecific mouse ascites for 15 min at 4°C and then washed once, 100 µl of culture fluid containing monoclonal antibody were added to the cell pellet and incubated at 4°C for 30 min. The cells were then washed twice with PBS, followed by the addition of 100 µl of fluorescein-conjugated F(ab')2 goat anti-human IgG or polyspecific immunoglobulins (Tago, Inc., Burlingame, CA) diluted in PSG 2.5%. The sample was incubated for 30 min at 4°C and then washed once in PBS. Following this, the pellet of live cells was resuspended in 250 µl PBS and then 250 µl of 1% (v/v) formaldehyde in PBS was added to fix the sample. The fixed cells were resuspended and stored up to 5 days until analysis at 4°C. Analysis was performed on an Epics C cell sorter (Coulter, Hialeah, FL). Cells fixed with formaldehyde after labeling with antibodies have been shown to retain, without significant alteration, prelysis findings upon flow cytofluorimetric analysis. Fixation permits storage of the sample for delayed evaluation and neutralizes human pathogens that might be present in the sample. Our own experiments and those of others have shown no effect of fixation on analysis under these conditions (12, 13). Negative controls for these experiments consisted of normal human sera diluted 1:1000 (approximately 10–20 µg/ml of IgG) and the monoclonal IgG immunoglobulins and antibodies 7C7 (IgG3 immunoglobulin) and F11DE2 (IgG; antitetanus human monoclonal antibody) (7). All negative controls gave the same results in multiple assays.

Radioimmunoprecipitation of Antigens. U937 cells were surface labeled by the lactoperoxidase method with [125I] (1.0 mCi/10^10 cells) and lysed with RIPA buffer (14). After centrifugation to remove nuclei and debris, the lysates were incubated with 25 µl of protein A-Sepharose-4B CL (Pharmacia, Uppsala, Sweden) that had been preincubated with 100 µl of goat anti-human immunoglobulins (Tago, Burlingame, CA), and 500 µl of HuMoab supernatant. After washing away unbound proteins, bound antigens were eluted by boiling in Laemmli buffer and subjected to SDS-PAGE under reducing conditions. RWLeu4 and U937 cells were metabolically labeled with [35S]methionine by culture in methionine-free media supplemented with 20% cell culture medium described above and 0.3 µCi of [35S]methionine/5 x 10^6 cells for 14 h. The cells were centrifuged and lysed with RIPA and the lysates immunoprecipitated with sepharose conjugated to goat anti-human IgG (Caltag, San Francisco, CA) that had been preincubated with HuMoabs. After unbound lysate protein had been removed by five washes in RIPA buffer, the bound antigen was eluted by boiling in Laemmli buffer and subjected to SDS-PAGE under reducing conditions. Unreduced eluates were diluted in RIPA buffer to reduce the concentration of SDS and then reprecipitated with the identical HuMoabs. These secondary immunoprecipitates were washed, eluted, reduced, and analyzed by SDS-PAGE as above.

**RESULTS**

Production of Human Monoclonal Antibodies. Peripheral blood mononuclear cells were obtained from a patient with CML in hematological remission following one cycle of intensive chemotherapy. The PBMs were depleted of CD8-positive T-cells and then distributed into 20 wells of a 24-well culture plate at 250,000 cells/well with EBV. Within 3 weeks all 20 of the cultures showed evidence of transformation. Supernatants from the EBV-transformed cultures were initially screened for reactivity with the human leukemic cell lines RWLeu4, HL60, and K562 by cell surface indirect immunofluorescence. Negative controls included monoclonal IgM and IgG immunoglobulins, sera, and antitetanus human monoclonal antibodies of IgG and IgM classes. Positive controls were not available. Four presumed polyclonal EBV-transformed B-cell cultures reacted with the acute promyelocytic cell line HL60 and the myeloid CML cell line RWLeu4, but were negative with the CML erythroleukemia cell line K562. The remaining 16 supernatants were negative with all three cell lines.

All four of the polyclonal EBV-transformed B-cell lines secreting reactive antibodies were expanded and three were fused with the human-mouse myeloma analogue HMMA2.11TG/O. The results of these fusions are shown in Table 1. The fusion efficiency was high and, in two fusions, the majority of the hybridomas secreted antibody reactive with the two myeloid leukemic cell lines. These results are in contrast to our previous
Table 1 Results of the fusion of HMMA2.11TG/O with antileukemic antibody secreting polyclonal B-cell lines

<table>
<thead>
<tr>
<th>Fusion Density</th>
<th>Wells</th>
<th>% Growth</th>
<th>AB</th>
<th>% AB</th>
<th>Cloned</th>
</tr>
</thead>
<tbody>
<tr>
<td>12,000</td>
<td>384</td>
<td>100</td>
<td></td>
<td>192b</td>
<td>100</td>
</tr>
<tr>
<td>10,000</td>
<td>384</td>
<td>99</td>
<td>3</td>
<td>1.6</td>
<td>1</td>
</tr>
<tr>
<td>5,200</td>
<td>192</td>
<td>21</td>
<td>21</td>
<td>52</td>
<td>2</td>
</tr>
</tbody>
</table>

* Fused EBV transformants/well.
† 192 wells each from fusions F37 and F38 were tested by indirect immunofluorescence.

Table 2 Reactivity of human monoclonal antibodies with cell lines of hematopoietic origin

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Cell line</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HL1.1</td>
</tr>
<tr>
<td>HL60</td>
<td>3+</td>
</tr>
<tr>
<td>RWLeu4</td>
<td>2+</td>
</tr>
<tr>
<td>BV173</td>
<td>0</td>
</tr>
<tr>
<td>K562</td>
<td>0</td>
</tr>
<tr>
<td>KG1</td>
<td>0</td>
</tr>
<tr>
<td>U937</td>
<td>4+</td>
</tr>
<tr>
<td>CEM</td>
<td>0</td>
</tr>
<tr>
<td>MOLT4</td>
<td>0</td>
</tr>
<tr>
<td>HPB-ALL</td>
<td>0</td>
</tr>
<tr>
<td>RAMOS</td>
<td>0</td>
</tr>
<tr>
<td>JD39</td>
<td>0</td>
</tr>
<tr>
<td>NALM1</td>
<td>0</td>
</tr>
<tr>
<td>NALM6</td>
<td>0</td>
</tr>
</tbody>
</table>

* Cell surface reactivity by indirect immunofluorescence above background. 0 = 0–10%, 1+ = 11–25%, 2+ = 26–50%, 3+ = 51–75%, 4+ = 76–100%.

studies with tetanus toxoid in which fusion efficiency with EBV transformants is slightly lower and the percentage of antibody-secreting wells substantially lower. Antibody-secreting hybridomas from each fusion were randomly selected, cloned and recloned. Recloned hybridomas were then used to generate culture supernatants containing human monoclonal antibodies which were used for subsequent studies. Antibody secretion by recloned hybridomas has been stable for periods of up to 6 months without recloning. Cultures were terminated at that time without loss of secretion for reasons of economy. The three human monoclonal antibodies have been designated HL1.1, HL2.1, and HL3.1. Isotype analysis indicates that they are of the IgG1, IgG3, and IgG1 isotypes, respectively. Routinely growing cultures were found to yield 11, 4, and 3.5 μg/ml of monoclonal antibody respectively in pooled supernatants.

Reactivity with Human Hematopoietic Cells. The three human monoclonal antibodies demonstrated identical patterns of cell surface reactivity with established human hematopoietic cell lines of diverse origin. As shown in Table 2, they react with a promyelocytic cell line (HL60), a promyelocytic CML cell line (RWLeu4), and a monoblastoid cell line (U937), but not with other myeloid or undifferentiated cell lines (KG1, BV173), an erythroleukemia CML cell line (K562), T-cell lines (CEM, MOLT4, HPB-ALL), Burkitt’s lymphoma cell lines (JD39, RAMOS), or pre-B-leukemia cell lines (NALM1, NALM6). Thus, the reactivity of these antibodies appears to be restricted to cell lines of myelomonocytic origin. Examples of the cytofluorographic reactivity of each of the antibodies with one of the cell lines, HL60, RWLeu4, or U937, are shown in Fig. 1.

The antibodies were further tested for reactivity with normal hematopoietic cells and leukemic cells from patients with diverse forms of chronic and acute leukemia. As shown in Table 3, no reactivity was observed with normal peripheral blood cells or bone marrow cells. Leukemic cells from two of seven patients with acute myelogenous or myelomonocytic leukemia and one patient with ALL were reactive with all three antibodies while leukemic cells from patients with other forms of leukemia were unreactive. Interestingly, the antibodies did not react with the chronic phase PBM of the patient from whom the hybridomas were derived, perhaps because of modulation of antigenic determinants by preexisting serum antibody or the later stage of differentiation of the circulating cells. Blast phase cells were not available from this patient. Analysis of the ALL patient’s cells with monoclonal antibodies demonstrated reactivity with a typical pre-B-cell leukemia pattern of CD10, CD19, and CD20 positivity. In addition, however, a fraction of the cells expressed MY7, a myeloid marker, indicating some lineage infidelity (15).

Radioimmunoprecipitation of Antigen. In order to assess the cell surface expression of these proteins, U937 cells were surface labeled with 125I, immunoprecipitated, and the immunoprecipitates resolved by SDS-PAGE. In addition to the known M, 72,000 Fc receptor, precipitated by the negative control IgG human monoclonal antitetanus antibody (16), the human anti-
leukemia antibodies precipitate a series of proteins at approximately Mr 42,000–54,000. A protein at approximately Mr 54,000 appeared to be well defined in HL2.1 and was not present in the control lane. Diffuse bands at Mr 42,000–54,000 were precipitated by HL 1.1 and 3.1 in association with a great deal of heavy chain protein (Fig. 2). In addition, light chains from all three human monoclonal antibodies migrated different distances on the SDS-gels in this experiment and the experiment described below (data not shown) confirming that antibodies HL1.1 and HL3.1 were uniquely different from one another although both are IgG1 isotype and have the same pattern of reactivity.

U937 cells, which expressed the largest cell surface amount of antigen, were metabolically labeled with [35S]methionine. Subsequent immunoprecipitation and reimmunoprecipitation of these metabolically labeled U937 cells demonstrated Mr 82,000 and 54,000 proteins specifically immunoprecipitated by all three antibodies and a Mr 63,000 protein precipitated by HL1.1 and HL3.1. Because of the low expression of these antigens, background was high despite reimmunoprecipitation (data not shown) and other approaches will be necessary to define these antigens.

DISCUSSION

In the present study we describe three human monoclonal antibodies that react with cell surface antigens on human myelomonocytic leukemia cell lines and blasts but not with hematopoietic cells from normal individuals or other leukemic patients and not with cell lines of other diverse hematopoietic origins. This highly restricted pattern of reactivity suggests that these antibodies react with differentiation or tumor-specific antigens present on myelomonocytic leukemia cells. All three antibodies, although derived from separate EBV transformants and having different heavy chain isotypes or light chains, seem to react with the same or highly associated antigens as shown by the pattern of cell surface reactivity and immunoprecipitation.

Auto-antileukemia antibody production has been observed and evaluated in a number of serological systems. Metzgar et al. and Garrett et al. described autoantibody production in leukemias and showed serological reactivity with both autologous and allogeneic leukemic blasts (2, 3). Mitchell et al. showed that cytophilic antibodies were present in the sera of leukemics and that specificity was easily demonstrable using these sera (1). Gutterman et al. demonstrated blastogenic responses to autologous leukemic blasts in association with membrane-bound immunoglobulin (4). Since these serological studies represent evaluations of polyclonal responses, the antigenic targets may be heterogenous. Targets of these polyclonal sera could include viral antigens, altered growth factor receptors, oncoprotein antigens, or abnormally expressed normal antigens. Alternatively, these antibodies could represent a phenomenon similar to systemic lupus erythematosus in which self antigens become targeted by the human humoral response possibly as a result of...
immune dysregulation induced by the disease or the therapy (17). Study of these antigens and antibodies might be important in understanding the pathogenesis of these diseases, the role of the host immune response in disease progression, and in the development of potentially therapeutic reagents. The development of murine monoclonal antibody technology shifted the emphasis away from studies of these autochthonous systems. Unfortunately, murine monoclonal antibody technology does not address the repertoire of the human auto-antitumor response. This is inherent in the murine system because the murine host preferentially reacts with differentiation and human specific antigens (7). Thus human monoclonal antibodies will be useful in capturing these antibodies so that we may study the repertoire of these responses and the impact of these antibodies and antigens on the progression of these diseases.

Solid tumor-reactive human monoclonal antibodies from patients with cancer have been reported by several investigators (18–23). Frequently, these human monoclonal antibodies, particularly IgM antibodies, have been found to react with a broad range of normal and abnormal cells. Occasionally, a normal intracellular component, such as cytokeratin, which is not normally antigenic, is found to be the target of antibody reactivity and confers an element of tumor tissue specificity (18, 22). Although IgG human monoclonal antibodies have been rare, the antisolid tumor human monoclonal IgG antibodies have had similar patterns of reactivity (20, 23). Our own studies have shown that IgM human monoclonal antibodies with diffuse cell surface reactivity to neoplastic and normal hematopoietic cells are relatively easy to obtain from both diseased and healthy individuals6,8 while tumor-specific antibodies may be both difficult to obtain and difficult to prove as being tumor specific.

Relatively specific IgG human monoclonal antibodies reactive with cell surface antigens on human leukemia cell lines and leukemic blasts have been reported by Andreasen and Olsson. They were able to prepare two separate IgG HuMoabs with similar reactivities from a patient with acute myelogenous leukemia and a patient with CML (24). The pattern of reactivity may have been a function of their screening method which eliminated reactivity with a variety of other hematopoietic cell lines. The antibody described by these coworkers reacted with an intracellular antigen in normal bone marrow cells and an abnormal M, 18,000 antigen expressed on the cell surfaces of leukemic cells. The antibodies described in the present study have a significantly different pattern of reactivity with cell lines and less broad reactivity with AML patients than those described by Andreasen and Olsson. In addition, all three antibodies immunoprecipitate proteins of M, 82,000 and 54,000 from metabolically labeled leukemic cells and a series of iodinatable cell surface-associated proteins in the range of M, 42,000–55,000. The data from these experiments are consistent with the M, 80,000 protein being an intracellular antigen while the M, 42,000–54,000 proteins are surface antigens. Alternatively, these antigens may be unrelated and share epitopes or may be disulfide-linked chains of a heterooligomeric protein. The differences also suggest that HL1.1 and HL3.1 are detecting identical antigens, while HL2.1 has a different but highly related specificity.

Unlike the system described by Andreasen and Olsson, in the presently described system for HuMoab production, preselection of EBV transformants on the basis of specificity, for fusion, is possible. Fusions were performed with three of the four antibody-producing transformants, but all four had the same reactivity pattern in the initial screening against HL60, K562, and RWLeu4. If reactivity patterns had varied, preselection for fusion would have been performed. This is an important potential advantage of the EBV transformation/fusion method with the high fusion efficiency cell line HMMA2.11TG/O. Of interest, fusion efficiency was 25–50% higher than that seen in our tetanus toxoid or collagen experimental systems, and equivalent to that seen in other antileukemia antibody experiments. Furthermore, compared to the tetanus or collagen systems, the frequency of hybridomas producing the desired antibody is 10–20 times greater in the antileukemia experiments. Taken together, these data support the notion that a large fraction of circulating B-cells in this leukemic patient were able to produce antibodies to these antigens and indicate that these antigens are highly immunogenic. One may speculate an important biological role for either the antigens or the humoral response.

In the present study, we have demonstrated that auto-antileukemia human monoclonal antibodies were readily obtainable from a patient with CML. These antibodies have highly restricted patterns of reactivity with established human leukemia cell lines and leukemic blasts, and lack significant reactivity with normal hematopoietic cells, suggesting that they react with tumor-specific antigen(s) on myelomonocytic leukemia cells, or highly restricted differentiation antigen(s). The biological importance and potential therapeutic use of these antibodies and antigens will be the subject of future studies.

REFERENCES


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