Immediate Early Response Gene X-1, a Stress-Inducible Antiapoptotic Gene, Encodes Cytotoxic T-Lymphocyte (CTL) Epitopes Capable of Inducing Human Leukocyte Antigen-A33-Restricted and Tumor- Reactive CTLs in Gastric Cancer Patients

Tetsuro Sasada,1 Hiroko Takedatsu,3 Koichi Azuma,3 Makoto Koga,3 Yoshiaki Maeda,4 Shigeki Shichijo,6 Hiroko Shoumura,1 Tatsuya Hirai,2 Arimichi Takabayashi,1 and Kyogo Itoh3

Departments of Surgery and Pathology, Takage-Kofukai Kitano Hospital, Osaka; 3Department of Immunology, Karume University School of Medicine, Karume; and 4Department of General Surgery, Hokkaido University Graduate School of Medicine, Sapporo, Japan

ABSTRACT

Peptide-based vaccine therapy, which is designed to elicit T-cell immunity against tumors, is an attractive approach for the treatment of cancer patients. To provide a scientific basis for peptide therapy, an increasing number of CTL-directed peptides have been identified, and some of them have been tried as antigen-specific immunotherapy in the past decade. Only a few studies, however, have been performed on such peptides restricted with alleles other than HLA-A2 and -A24. In the present study, we show that immediate early response gene X-1 (IEX-1), a stress-inducible protein associated with the regulation of cell proliferation and apoptosis, produces antigenic epitopes recognized by 850B-CTLs, HLA-A33-restricted CTLs newly established from T cells infiltrating into gastric adenocarcinoma. The IEX-1 gene was highly expressed in most cell lines and tissues from various types of cancer at both the mRNA and protein levels. However, it was not expressed at the protein level in any normal epithelium or connective tissues tested. Three IEX-1-derived peptides at positions 47–56, 61–69, and 65–73, which were recognized by the 850B-CTLs, could induce CD8+ peptide-specific CTL reaction to tumor cells from HLA-A33+ gastric cancer patients and other epithelial cancer patients, but not from healthy donors, in an HLA class I-restricted manner. Because increased expression of IEX-1 is suggested to be involved in the resistance to apoptosis and in the proliferation of cancer cells, these antigenic peptides could be potent candidates for peptide-based specific immunotherapy against HLA-A33+ gastric cancer and other epithelial cancers.

INTRODUCTION

There is growing evidence that human tumors express antigenic peptides recognized by CTLs, and some of these peptides have been used as peptide vaccines for cancer patients with HLA-A2 or -A24 alleles (1–7). In contrast to the many reports on epitope peptides recognized by HLA-A2 or -A24 CTLs (8–11), information on the alleles (1–7). In contrast to the many reports on epitope peptides recognized by HLA-A2 or -A24 CTLs (8–11), information on the antigens and peptides recognized by HLA-A33-restricted CTLs is very limited (12, 13). This lack of information is hampering the development of a peptide-based specific immunotherapy for HLA-A33+ cancer patients, regardless of the relatively wide expression of the HLA-A33 allele in various ethnic groups around the world (14, 15). Gastric cancer (GC) is one of the most commonly occurring malignancies in the world (16). The prognosis of this disease is generally good if it is detected at an early stage, but the prognosis for the disease when discovered at an advanced stage, particularly for scirrhous-type cancer, is extremely poor despite recent significant progress in conventional therapeutic modalities. The development of novel therapeutic modalities, such as peptide-based specific immunotherapy, is therefore needed for the treatment of patients at advanced stages of disease. Indeed, we recently reported that peptide vaccination prolonged the overall survival of HLA-A24 or -A2 patients with scirrhous-type GC (4). To identify CTL epitope peptides, we have established a new HLA-A33-restricted CTL line from the tumor-infiltrating lymphocytes (TILs) of a patient with scirrhous-type GC and identified a new gene, immediate early response gene X-1 (IEX-1; Ref. 17), which codes for tumor antigens. We have demonstrated that the three IEX-1-derived peptides are capable of inducing HLA-A33-restricted CTL activity reactive to tumor cells in the peripheral blood mononuclear cells (PBMCs) of patients with epithelial cancer. The identified antigenic peptides may be clinically useful as appropriate target molecules in specific immunotherapy for HLA-A33+ cancer patients.

MATERIALS AND METHODS

Generation of the 850B-CTL Line. The HLA-A33-restricted and tumor-specific CTL line (850B-CTL) was newly established from the TILs of a patient with scirrhous-type GC (HLA-A*2402/A*3303, B7/B44, Cw7/Cw14) by the method reported previously (11). The established CTL line was tested for its responses to various cancer and normal cells by use of a 6-h 3H-release assay and by measurement of IFN-γ with an ELISA, as reported previously (11). The phenotype of the CTL line was examined by an immunofluorescence assay with FITC-conjugated anti-CD3, -CD4, or -CD8 monoclonal antibodies (mAbs). For the inhibition of CTL activity, 100 μg/ml each of anti-HLA class I (W6/32, IgG2a); anti-CD8 (Nu-Ts/c, IgG2a); anti-HLA-A24 (0041HA, IgG2a); anti-CD4 (Nu-Thi, IgG1); anti-HLA class I B, C (B1-25, IgG2a); anti-HLA class II (H-DR1, IgG2a); and anti-CD14 (MLM-H14, IgG1) mAbs were used as reported previously (11). The cell line cells used for this experiment were as follows: gastric adenocarcinoma (MKN-28, MKN-45, SSTW-9, KATO-III, KWS, and HGC-27), lung carcinoma (LC-1 and QG-56), head and neck carcinoma (KUMA-1), colon adenocarcinoma (SW620 and COLO 201), pancreatic adenocarcinoma (Panc-1), and human chronic myelogenous leukemia (K562). The HLA class I genotypes of these tumor cells are described elsewhere (11). The expression of HLA class I or HLA-A33 antigens on these cells was measured by flow cytometry on a FACScan (Becton Dickinson, San Jose, CA), and then the tumor cells were stained with anti-HLA class I (W6/32) mAb, which recognizes a monomorphic region of HLA class I molecule, or anti-HLA-A33 mAb (IgM; One Lambda, Canoga Park, CA), which recognizes a polymorphic region of HLA-A33 molecule as reported previously (11). Identification of the IEX-1 Gene. An expression gene-cloning method was used to identify the gene coding for the tumor antigen recognized by the 850B-CTL line, as reported previously (11). cDNA from LC-1 was inserted into the expression vector pSV-SPORT-6 (Invitrogen, San Diego, CA). HLA-A*3303 or HLA-A*2601 cDNA was obtained by reverse transcription-PCR with RNA from KUMA-1 or KE-4 cells, respectively, and was cloned into the eukaryotic expression vector pCR3.1 (Invitrogen). DNA sequencing was performed by a dideoxynucleotide sequencing method using a DNA sequencing kit and ABI PRISM 377 DNA Sequence (Perkin-Elmer, Foster, CA).

Northern Blot Analysis and Immunohistochemistry. The expression of IEX-1 mRNA on various tumor or normal tissues (Multiple Tissue Northern Blot Analysis and Immunohistochemistry)
Establishment of an HLA-A33-Restricted, Tumor-Specific CTL Line. A CTL line (850B-CTL) was established from the TILs of a GC patient and was characterized by testing its reactivity to various cancer and normal cells as determined by both IFN-γ production and 6-h 51Cr-release assay. As shown in Fig. 1A, this CTL line produced significant levels of IFN-γ in the presence of the HLA-A33+ epithelial cancer cell lines LC-1 and KUMA-1 and lower levels of IFN-γ in response to QG56 (A26), Panc-1 (A02/11), and HG27 (A02/24); it did not produce any IFN-γ in response to the other three HLA-A33+ target cell lines tested. The 850B-CTL cell line also showed significant levels of cytotoxicity against LC-1 and KUMA-1 cells but not against any of the five HLA-A33+ target cells, COS-7 cells, the natural killer target cell line K562, or HLA-A33+ phytohemagglutinin-activated normal T cells (phytohemagglutinin-blast cells) from the PBMCs of healthy donors (Fig. 1B). The expression levels of HLA-A33 of these tumor cells were not largely different from those of the normal cells (data not shown). The production of IFN-γ by the 850B-CTL cell line in response to HLA-A33− LC-1 cells was significantly inhibited by 100 μg/ml anti-HLA class I or anti-CD8 mAb but not by anti-HLA-BC, anti-HLA class II, anti-HLA-A24, anti-CD4, or an isotype-matched irrelevant anti-CD14 mAb (Fig. 1C). The phenotype of the 850B-CTL cell line (>98%) was CD3+ CD4− CD8+ (data not shown). These results indicate that the 850B-CD8+ CTL line largely consisted of T cells with HLA-A33-restricted, tumor-reactive.

RESULTS

Induction of CTLs by Peptides. Among possible peptide sequences with motifs for binding to the HLA-A33 molecule (18, 19) in the deduced amino acid sequence of IEX-1, eight different peptides that showed stronger binding activity for HLA-A33 in a computer analysis (Bioinformatics and Molecular Analysis Section, NIH, Bethesda, MD) were used. Peptides with a purity of >95% were obtained from Biologica (Nagoya, Japan). For the peptide-binding assay, RMA-S-A33 cells, RMA-S tap (transporter-associated peptide processing)-deficient mouse lymphoma cells stably transfected with HLA-A*3303 cDNA, were used. Briefly, the cells were incubated at 26°C for 18 h and were suspended in Opti-MEM containing 3 μg/ml human β2-microglobulin and 100 μg/ml peptides, followed by incubation at 26°C for 3 h and at 37°C for 3 h. The cells were then incubated with anti-HLA-A33 mAb at 4°C for 30 min, followed by incubation with FITC-conjugated rabbit antimouse IgM antibody (Cappel, Aurora, OH) at 4°C for 30 min. The cells were analyzed by FACScan, and their binding activity was evaluated by the mean fluorescence intensity. Cells pulsed with TRP2−197 peptide were used as a control (12). For the detection of antigenic peptides recognized by the 850B-CTL line, C1R-A33 cells were used as reported previously (13). IFN-γ production in the culture supernatants was measured by an ELISA.

Induction of CTLs by Peptides. After written informed consent was obtained, PBMCs from HLA-A33+ cancer patients (n = 4; 2 GC patients, 1 lung cancer patient, and 1 prostate cancer patient), and 5 HLA-A33+ healthy donors served as subjects for the CTL induction assay. PBMCs (1 × 10⁶ cells/well) were incubated with each peptide in the wells of a 96-well microculture plate (Nunc, Roskilde, Denmark), as reported previously (13). On the 14th day of the culture, the cells were tested for their ability to produce IFN-γ in response to CIR-A33 pulsed with a corresponding peptide or a negative-control peptide (HIV). After an 18-h incubation, the supernatant was collected for the measurement of IFN-γ by ELISA. The PBMCs showing a positive response were further cultured with interleukin-2 alone for 10–14 days for a standard 6-h 51Cr-release assay (13). For the inhibition test, 20 μg/ml each of anti-HLA class I (W6/32, IgG2a), anti-HLA-A2 (BB7.2, IgG2b), anti-CD8 (Nu-Ts/c, IgG2a), anti-HLA class II (H-DR1, IgG2a), and anti-CD4 (Nu-Th/i, IgG1) mAb were used. Anti-CD14 (JML-H14, IgG2a) mAb served as a control.

Statistical Analysis. A two-tailed Student’s t test was used for statistical analysis throughout the study.
cytotoxicity, although it contained a few T cells that produced IFN-γ without apparent HLA class I-A restriction or with HLA-A24 restriction.

Identification of a Gene Recognized by 850B-CTLs. A total of 10 × 10⁴ cDNA clones from the cDNA library of LC-1 tumor cells were tested for their ability to stimulate IFN-γ production by the 850B-CTL cell line when cotransfected with HLA-A*3303 into COS-7 cells. After repeated experiments for several candidate clones, one clone (clone 1) was confirmed to encode a tumor antigen recognized by the HLA-A33-restricted 850B-CTLs. As shown in Fig. 2A, COS-7 cells transfected with clone 1 and HLA-A*3303, but not with clone 1 and HLA-A*2601 as a negative control, induced IFN-γ production in 850B-CTLs in a dose-dependent manner. The expression of HLA class I antigens by HLA-A26-transfected COS-7 cells was not significantly different from expression by HLA-A33-transfected COS-7 cells when stained with anti-HLA-class I mAb (Fig. 2B). In contrast, COS-7 cells transfected with either clone 1 or HLA-A*3303 alone were not recognized by the 850B-CTLs (Fig. 2A). The other clones from the LC-1 cDNA library also failed to induce IFN-γ production in 850B-CTLs when cotransfected with HLA-A*3303 into COS-7 cells. The results of the experiments on clone 2, as a negative control, are shown in Fig. 2A. The nucleotide sequence of clone 1 was found by a search of GenBank (GenBank accession no. NM003897) to be completely identical to that of IEX-1, which has been reported to be a stress-inducible antiapoptotic gene (17).

Overexpression of IEX-1 Gene in Tumor Tissues. The expression of IEX-1 mRNA in normal and cancer cells was investigated by Northern blot analysis. As shown in Fig. 3A, a band of ~1.3 kb was clearly detected in all of the normal tissues tested except the brain (Fig. 3A, Lane 1), with much higher expression in the heart (Fig. 3A, Lane 2), kidney (Fig. 3A, Lane 7), lung (Fig. 3A, Lane 11), and peripheral blood lymphocytes (Fig. 3A, Lane 12), and lower expression in the thymus (Fig. 3A, Lane 5), spleen (Fig. 3A, Lane 6), liver (Fig. 3A, Lane 8), and small intestine (Fig. 3A, Lane 9). In addition, this gene was highly expressed in most of the adenocarcinoma and squamous cell carcinoma cell lines tested, except for the HCG27 GC cell line (Fig. 3B, Lane 5), from various organs, including the stomach (Fig. 3B, Lanes 2–4 and 12), lung (Fig. 3B, Lanes 6 and 7), head and neck (Fig. 3B, Lanes 6 and 7), pancreas (Fig. 3B, Lane 8), and colon (Fig. 3B, Lanes 10 and 11). These results indicate that this gene is overexpressed in the majority of cancer cells and also is expressed in most normal tissues at various levels. To determine the expression of IEX-1 at the protein level, immunohistochemistry was performed in cancer tissues from various organs. As shown in Fig. 3C, the IEX-1 protein was selectively expressed in cytoplasm of all of the GC cells, but not in the surrounding normal epithelium or connective tissues. IEX-1 protein was also selectively expressed in the cytoplasm of the various

<table>
<thead>
<tr>
<th>Table 1 Binding activity of immediate early response gene X-1-1-derived peptides to RMA-S-A33 cellsa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptide</td>
</tr>
<tr>
<td>(−), 26°C</td>
</tr>
<tr>
<td>(−), 37°C</td>
</tr>
<tr>
<td>IEX20-28</td>
</tr>
<tr>
<td>IEX43-51</td>
</tr>
<tr>
<td>IEX47-56</td>
</tr>
<tr>
<td>IEX53-61</td>
</tr>
<tr>
<td>IEX54-63</td>
</tr>
<tr>
<td>IEX61-69</td>
</tr>
<tr>
<td>IEX64-73</td>
</tr>
<tr>
<td>IEX65-73</td>
</tr>
<tr>
<td>TRP2-197</td>
</tr>
</tbody>
</table>

a Binding activity of immediate early response gene X-1-1-derived peptides to HLA-A33 molecules was evaluated by the mean fluorescence intensity after staining of the RMA-S-A33 cells pulsed with the indicated peptide with anti-HLA-A33 monoclonal antibody.
b MFI, mean fluorescence intensity; IEX, immediate early response gene X-1.
types of cancer tissues, including breast (Fig. 3D), lung (Fig. 3E), and colon (data not shown) cancer tissues. In contrast, it was not expressed in the surrounding normal epithelium or connective tissues of breast, lung, and colon. The only exception among normal cells tested was TILs, which expressed the IEX protein (data not shown).

Identification of IEX-1-Derived Antigenic Peptides Recognized by 850B-CTLs. To identify the IEX-1-derived CTL epitopes, we determined eight possible peptide sequences with motifs for binding to the HLA-A33 molecule in the deduced amino acid sequence of IEX-1 in a computer analysis. Each of the eight synthetic peptides was loaded into HLA-A33-transfected cells (RMA-S-A33) at a concentration of 100 μM, and the binding affinities of these peptides were analyzed. As shown in Table 1, all eight peptides and a reference peptide (TRP2-197) were able to bind to RMA-S-A33 cells, but with slightly different affinities. We next incubated C1R-A33 cells with these eight peptides at a concentration of 1 μM and tested their ability to induce IFN-γ production by the 850B-CTLs. Three of these peptides, IEX47–56, IEX61–69, and IEX65–73, induced significant levels of IFN-γ production (Fig. 4A) in a dose-dependent manner (Fig. 4B). The optimum concentrations varied for each peptide and were in the range of 0.1–1 μM (Fig. 4B); the optimum concentration was not dependent on peptides’ binding affinities for the HLA-A33 molecule, determined with RMA-S-A33 cells (Table 1).

Induction of CTLs by IEX-1-Derived Peptides. IEX47–56, IEX61–69, and IEX65–73 peptides were then tested for their ability to induce HLA-A33-restricted, tumor-specific CTLs in the PBMCs of four HLA-A33+ epithelial cancer patients (gastric, lung, or prostate cancer). The PBMCs from these cancer patients, stimulated by each of these three peptides, in most cases tested produced significant amounts of IFN-γ in response to C1R-A33 cells loaded with the corresponding peptides (Fig. 5). In contrast, PBMCs from none of the five healthy donors tested produced significant amounts of IFN-γ in response to C1R-A33 cells loaded with the corresponding peptides even after stimulation with each of these peptides (data not shown).

We next examined CTL activity against tumor cells in the patients’ PBMCs stimulated with IEX-1-derived peptides by use of a 6-h 51Cr-release assay. The PBMCs stimulated with each of the three IEX-1-derived peptides, but not those with a negative control peptide (IEX43–51), showed significant levels of cytotoxicity against the HLA-A33+ IEX-1+ LC-1 tumor cells, but not against the HLA-A33+ HGC27 or QG56 cells in any of the cases tested (Fig. 6A). In contrast, PBMCs stimulated with a negative control peptide (IEX43–51) showed no specific CTL activity (Fig. 6A). Collectively, each of the IEX47–56, IEX61–69, and IEX65–73 peptides had the ability to induce HLA-A33-restricted CTL activity toward tumor cells in PBMCs in most of the cases tested, indicating that the three peptides identified, IEX47–56, IEX61–69, and IEX65–73, are antigenic epitopes capable of inducing HLA-A33-restricted, tumor-specific CTLs in PBMCs from patients with epithelial cancer.

The restriction and peptide specificity of the cytotoxicity were confirmed by inhibition and competition assays, respectively. In all of the cases tested, the levels of cytotoxicity of these peptide-stimulated PBMCs were significantly inhibited by anti-HLA class I or anti-CD8 mAb, but not by the other mAbs tested (Fig. 6B). The cytotoxicity was also inhibited by the addition of the corresponding peptide-pulsed C1R-A33 cells, but not by addition of the HIV peptide-pulsed cells in all of the cases tested (Fig. 6C). These results suggest that the CTL activity against tumor cells was largely mediated by the peptide-reactive CD8+ T cells in an HLA class I-restricted manner.

DISCUSSION

The present study demonstrates that IEX-1 encodes tumor antigenic epitopes recognized by HLA-A33-restricted, tumor-specific CTLs, IEX-1, also known as p22/PRG1 (20), Dif-2 (21), or the mouse homolog
IEX-1 is a stress-inducible gene and is involved in the regulation of cell cycle progression and apoptosis (17). IEX-1 has been reported to play a key role in the cellular resistance to apoptosis induced by various apoptotic triggers, such as tumor necrosis factor and Fas (23), and to accelerate cell cycle progression in some cell lines (24–26). IEX-1 transgenic mice show decreased apoptosis in activated T cells, resulting in the accumulation of effector/memory-like T cells and the development of splenomegaly and lymphadenopathy, and are more susceptible to the development of a lupus-like autoimmune disease than their non-transgenic littermates (27). Garcia et al. (28) showed that IEX-1 is a new type of substrate for extracellular signal-regulated kinase, one of the mitogen-activated protein kinases, and has a dual role in extracellular signal-regulated kinase signaling by acting both as an extracellular signal-regulated kinase downstream effector mediating survival and as a regulator of extracellular signal-regulated kinase activation. These findings suggest that increased expression of IEX-1 may contribute to malignant transformation in cancer cells through a lack of apoptosis and/or enhanced proliferation.
Expression of IEX-1, a stress-inducible protein, can be rapidly activated by several cellular stresses, including irradiation, growth factors, viral infection, inflammatory cytokines such as tumor necrosis factor-α and interleukin-1β, lipopolysaccharides, and steroid hormones (17). Although IEX-1 was originally identified as a nuclear factor-kB/rel target gene (23), the IEX-1 promoter contains several consensus sequences for other transcription factors, such as p53, SP-1, and c-Myc (17). For example, recent studies have suggested that mutation of p53, which is common in tumor cells, up-regulates IEX-1 expression (29). In the present study, we have shown that IEX-1 is highly expressed in most of the cancer cell lines or cancer tissues tested at both the mRNA and protein levels. In contrast, IEX-1 was undetectable at the protein level in any of the normal tissues tested regardless of its expression in normal tissues at the mRNA level. In view of the finding that IEX-1 is strongly expressed in rapidly growing cells (25), IEX-1 may be one of the ideal target molecules in the treatment of patients with cancer. In particular, because irradiation and several chemotherapy-drug peptides have been reported to induce IEX-1 expression at relatively high levels (26, 30), a novel therapy, such as a specific immunotherapy, that targets the IEX-1 molecule may be an attractive approach to the treatment of patients with chemotherapy- or radiotherapy-resistant cancers.

Because IEX-1 is also expressed in normal tissues at the mRNA level, particularly in the heart, kidney, lung, and peripheral blood lymphocytes, these organs may be possible targets for the adverse effects of specific immunotherapy with IEX-1-derived antigenic epitopes. However, the present study showed that neither the 850B-CTL line nor the CTLs induced by the IEX-1-derived peptides lysed phytohemagglutinin-activated normal HLA-A33+ T cells, even in the presence of excess amounts of the corresponding peptide in culture. No severe adverse effects on normal tissues or organs have been observed in our clinical trials with peptide vaccines derived from tumor rejection antigens, some of which are ubiquitously expressed in normal tissues and organs (4–7). Processing of the antigenic peptides in proteasomes or post-translational modification of the peptides in cancer cells may be a little different from these processes in normal cells (8, 31). Further studies, including determination of the molecules involved in the resistance to lysis in normal cells, will be needed to clarify these issues.

The HLA-A33-restricted CTL line used in this study was established from TILs of a GC patient (HLA-A*2402/A*3303) and consisted of bulk-cultured CTLs. Therefore, this CTL line should contain a few CTLs reactive to HLA-A24+ tumor cells. However, the cross-reactivity of this CTL line with HLA-A24 molecules could be functionally negligible because anti-HLA-A24 mAb scarcely inhibited IFN-γ production by the CTL line in response to LC-1 tumor cells (Fig. 1C). Furthermore, this CTL line failed to show significant levels of cytotoxicity to HLA-A24+ tumor cells in the 51Cr-release assay (Fig. 1B).

Among the eight peptides tested, only the peptides IEX47–56, IEX61–69, and IEX65–73 were recognized by the 850B-CTL cell line. All eight peptides tested had similar binding activities toward HLA-A33 molecules; thus, this result cannot be explained simply by differences in the binding affinities between the peptides and HLA-A33 molecules. Only the three peptides that were recognized by 850B-CTLs can be generated through the natural antigen-processing machinery in vivo and expressed in complex with HLA-A33 molecules on the cell surfaces of antigen presenting cells or tumor cells. Indeed, each of the three peptides induced peptide-specific CTLs in the PBMCs of HLA-A33+ cancer patients in most of the cancer patients but in none of the healthy donors tested. This may be explained by the different frequencies of specific CTL precursors reacting to the peptides in the circulation of cancer patients (10, 11). This discrepancy could be explained by the fact that the IEX protein is preferentially expressed in cancer cells but not in normal epithelial cells or cells of connective tissues. IEX47–56 induced peptide-specific CTls from all four of the patients tested, whereas the other two peptides induced CTLs in three of the four patients. This may be partly due to a difference in precursor frequencies of each peptide-specific CTL in the circulation of each cancer patient. The profiles of peptide-specific CTLs could be different from patient to patient.

HLA-A33 is one of the most common HLA-A alleles in Asians and blacks and is found in 13% of Japanese, 14% of Koreans, 4% of Caucasians, and 16% of blacks (14, 15). The three IEX-1-derived peptides induced HLA-A33-restricted, tumor-specific CTLs in the PBMCs of patients with GC and other epithelial cancers. Because IEX-1 is highly expressed in cancer tissues, these peptides might be appropriate target molecules for specific immunotherapy for HLA-A33+ cancer patients.

REFERENCES

20. Schafer H, Trauzold A, Siegel EG, Folsch UR, Schmidt WE. PRG1: a novel monocyte/macrophage differentiation-dependent gene that is responsive to...


Immediate Early Response Gene X-1, a Stress-Inducible Antiapoptotic Gene, Encodes Cytotoxic T-Lymphocyte (CTL) Epitopes Capable of Inducing Human Leukocyte Antigen-A33-Restricted and Tumor-Reactive CTLs in Gastric Cancer Patients

Tetsuro Sasada, Hiroko Takedatsu, Koichi Azuma, et al.


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/64/8/2882

Cited articles
This article cites 27 articles, 13 of which you can access for free at:
http://cancerres.aacrjournals.org/content/64/8/2882.full#ref-list-1

Citing articles
This article has been cited by 2 HighWire-hosted articles. Access the articles at:
http://cancerres.aacrjournals.org/content/64/8/2882.full#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.