Identification of cIAP1 As a Candidate Target Gene within an Amplicon at 11q22 in Esophageal Squamous Cell Carcinomas

Issei Imoto, Zeng-Quan Yang, Atiphan Pimkhaokham, Hitoshi Tsuda, Yutaka Shimada, Masayuki Imamura, Misao Ohki, and Johji Inazawa

Department of Molecular Cytogenetics, Medical Research Institute, Tokyo Medical & Dental University, Tokyo 113-8510, Japan [J. I., Z.-Q. Y., A. P., J. I.]; Second Department of Pathology, National Defense Medical College, Saitama 359-8513, Japan [H. T.]; Department of Surgery, Surgically Basic Medicine, Kyoto University Graduate School of Medicine, Sakyō-ku, Kyoto 606-8507, Japan [Y. S., M. I.]; and Cancer Genomics Division, National Cancer Center Research Institute, Chuo-ku, Tokyo 104-0045, Japan [M. O.]

Abstract

Amplification of chromosomal DNA is thought to be one of the mechanisms that activate cancer-related genes in tumors. In a recent study, we identified high copy-number amplification at 11q21-q23 in cell lines derived from esophageal squamous cell carcinomas (ESCs) using comparative genomic hybridization. Because 11q21-q23 amplification has been reported in tumors of various other types as well, gene(s) associated with tumor progression may lie within this chromosomal region. To identify the most likely target(s) for amplification at 11q21-q23, we determined the extent of the amplicon by fluorescence in situ hybridization and then analyzed ESC cell lines for expression levels of 11 known genes and one uncharacterized transcript present within the 1.8-Mb commonly amplified region. Only cIAP1, a member of the IAP (inhibitor of apoptosis) gene family, was consistently overexpressed in cell lines that showed amplification. Additionally, the cIAP1 protein was overexpressed in the primary tumors from which those cell lines had been established. The ESC cell lines with cIAP1 amplification were resistant to apoptosis induced by chemotherapeutic reagents. An increase in cIAP1 copy number was also detected in 4 of 42 (9.5%) primary ESC tumors that were not related to the cell lines examined. Because inhibition of apoptosis seems to be an important feature of carcinogenesis, cIAP1 is likely to be a target for 11q21–23 amplification and may be involved in the progression of ESC, as well as other malignancies.

Introduction

Gene amplification, a phenomenon characteristic of numerous human cancers, appears to be a key mechanism whereby a cancer cell activates molecules that confer a selective advantage (1). Many oncogenes or other cancer-related genes have been identified in amplified chromosomal regions. Therefore, characterization of high-copy-number amplifications and the genes affected by them represents an excellent route toward identification of novel genes involved in carcinogenesis regardless of the type of tissue involved, although no specific gene has been proposed as a target.

In the study reported here, we performed a detailed molecular characterization of the 11q21-q23 amplicon using ESC cell lines, with the goal of identifying gene(s) involved in tumorigenesis. By determining levels of amplification and expression of 12 transcribed elements located in this amplicon, we successfully identified one candidate, cIAP1, a gene that encodes an inhibitor of apoptosis molecule. Cell lines that overexpressed this gene were resistant to the apoptosis induced by chemotherapeutic reagents. Because any mechanism that aberrantly prolongs the life span of a cell may contribute to carcinogenesis, our findings indicate that cIAP1 is a potential target for 11q21–23 amplification on the basis of both position and function.

Materials and Methods

ESC Cell Lines and Tumors. All 31 human ESC cell lines of the KYSE series had been established from surgically resected tumors (13) and maintained in RPMI 1640 supplemented with 10% FCS. Data from CGH analyses involving 29 of those lines have been reported elsewhere (7). ESC tumor samples from 42 patients were provided by the Kyoto University Hospital, with written consent from each patient in the formal style and after approval by the local ethics committee.

FISH. Metaphase chromosome slides were prepared, and FISH experiments were carried out in the manner described previously (14, 15). The locations of BACs (RPCI-11 library) within the region of interest were compiled from information archived by the UCSC4 and the National Center for Biotechnology Information.5 Relative positions of the selected BACs on a map of the 11q22 region are indicated in Fig. 1. Probes were labeled by nick-translation with biotin-16-dUTP or digoxigenin-11-dUTP (Roche Diagnostics, Tokyo, Japan). Chromosomal in situ suppression hybridization and fluorescent detection of hybridization signals were carried out as described elsewhere (14, 15). The copy number and molecular organization of the region of interest were assessed according to the hybridization patterns observed on both metaphase: SRO, smallest amplified region of overlap; IAP, inhibitor of apoptosis; MALT, mucosa-associated lymphoid tissue; GAPDH, glyceraldehyde-3-phosphate dehydrogenase.

4 Internet address: http://genome.ucsc.edu/.

Received 5/1/01; accepted 7/31/01.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Supported by Grants-in-Aid for Scientific Research on Priority Areas (C) from the Ministry of Education, Culture, Sports, Science and Technology, Grants-in-Aid from the Ministry of Health and Welfare of Japan, and in part by a grant from the Organization for Pharmaceutical Safety and Research.

To whom requests for reprints should be addressed, at Department of Molecular Cytogenetics, Medical Research Institute, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8510, Japan. Phone: 81-3-3803-5820; Fax: 81-3-3803-0244; E-mail: johinaz.cgen@mri.tmd.ac.jp.

The abbreviations used are: ESC, esophageal squamous cell carcinoma; CGH, comparative genomic hybridization; FISH, fluorescence in situ hybridization; BAC, bacterial artificial chromosome; DAPI, 4',6'-diamidino-2-phenylindole; HSR, homogeneously staining region; FIC, fluorescent immunocytochemistry; IHC, immunohistochemistry; UCSC, University of California at Santa Cruz; cDDP, cis-platinum; CPT, camptothecin; SRO, smallest amplified region of overlap; IAP, inhibitor of apoptosis; MALT, mucosa-associated lymphoid tissue; GAPDH, glyceraldehyde-3-phosphate dehydrogenase.
aphase and interphase chromosomes. Precise localization of each BAC was confirmed using normal metaphase chromosomes.

Southern-, Dot-, and Northern-Blot Hybridizations. We used Southern and Northern blotting to investigate the status of amplification and overexpression of 11 known genes and one uncharacterized transcript that lies within the 11q22 amplicon we had observed in ESC cell lines (Fig. 1A; Table 1). ATM (cDNA probe: clone 1367928) telomeric to the 11q22 amplicon was used as a reference in each analysis (Fig. 1A). For Southern blots, 10 μg of genomic DNA from each cell line or from normal lymphocytes were digested with EcoRI and separated on 0.8% agarose, then transferred onto a nylon membrane (BIODYNE B; Nihon Pall, Tokyo, Japan). For analyzing primary ESC tissues, we prepared Southern blots with 5 μg of genomic DNA or used dot blots, because the amount of available DNA was limited. For dot blots, 2 μg of DNA from each tumor, cell line, or normal lymphocyte was denatured with 0.4 N NaOH, then transferred to a nylon membrane (BIODYNE B; Nihon Pall). For Northern blots, 10 μg of total RNA extracted from each cell line was electrophoresed in a 1.0% agarose/0.67 M formaldehyde gel and transferred to a positively charged nylon membrane (Hybond N+; Amersham Pharmacia Biotech, Tokyo, Japan). Membranes were hybridized under appropriate conditions with [α-32P]-dCTP-labeled cDNA probes prepared from expressed-sequence tag clones (Table 1) purchased from Incyte Genomics, Inc. (St. Louis, MO). The blots were washed in a solution of 0.1XSSC/0.1% SDS before exposure to X-ray film for 24–84 h at −80°C.

FIC and IHC. We detected expression of cIAP1 protein in ESC cell lines by indirect FIC, as described elsewhere (16, 17). In brief, cultured cells were fixed with acetone/methanol (1:1 volume for volume), blocked with antibody-dilution buffer (1% BSA in PBS), and incubated with 1 μg/ml antihuman cIAP1 polyclonal antibody (H-83; Santa Cruz Biotechnology, Santa Cruz, CA) for 60 min at room temperature. Normal rabbit serum was used as a negative control for the first antibody. Binding was detected by incubation with FITC-conjugated goat antirabbit IgG (ICN Pharmaceuticals, Aurora, OH) diluted 1:200 with antibody-dilution buffer. The cells were counterstained with DAPI and observed under a fluorescence microscope (Nikon, Tokyo, Japan).

Expression of cIAP1 protein in formalin-fixed, paraffin-embedded tissue sections from primary ESC tumors was detected by indirect IHC, as described elsewhere (18). Dewaxed and rehydrated sections were incubated in 3% H2O2 for 30 min, blocked with 10% normal horse serum, and incubated with a rabbit polyclonal antibody against cIAP1 (1:500 dilution; Santa Cruz Biotechnology). The sections were then incubated with a biotinylated secondary antibody, followed by avidin-biotin-peroxidase complex (Nichirei, Tokyo, Japan) for immunoreaction. The chromagen was diaminobenzidine (DAB) (Nichirei) and the sections were counterstained with hematoxylin.

Table 1 Genes and transcripts analyzed in the present study

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Gene/transcript</th>
<th>GenBank accession no.</th>
<th>Probe for hybridization</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIAA1377</td>
<td>NADH-ubiquinone oxido-reductase subunit B14.5B</td>
<td>XM_006268</td>
<td>AA09011311</td>
</tr>
<tr>
<td>NDUFC2</td>
<td>Enamelysin</td>
<td>AL050278</td>
<td>R05628</td>
</tr>
<tr>
<td>MMP20</td>
<td>Matrilysin</td>
<td>X07819</td>
<td>AW593141</td>
</tr>
<tr>
<td>MMP7</td>
<td>Cellular inhibitor of apoptosis 1</td>
<td>XM_006268</td>
<td>AW95584</td>
</tr>
<tr>
<td>MMP10</td>
<td>Neutrophil collagenase</td>
<td>NM_002424</td>
<td>AW236358</td>
</tr>
<tr>
<td>MMP12</td>
<td>Stromelysin1, progelatinase</td>
<td>XM_006269</td>
<td>AB129878</td>
</tr>
<tr>
<td>MMP13</td>
<td>Stromelysin1</td>
<td>XM_006270</td>
<td>AA182830</td>
</tr>
<tr>
<td>MMP14</td>
<td>Collagenase 3</td>
<td>XM_006272</td>
<td>AA586839</td>
</tr>
</tbody>
</table>

Fig. 1. A, map of the 11q22 region between two markers, R94982 and ATM. The top scale shows the ordering of selected sequence-tagged site (STS) markers mapped on this region. The 20 BACs used as probes in FISH analysis are indicated as horizontal open bars. The position of each STS, and the position and relative length of each BAC, were compiled from information archived by the UCSC and the National Center for Biotechnology Information. Genes and uncharacterized transcripts mapped in this region, including the 12 transcripts we analyzed (boxed) and ATM as reference gene, are listed on the bottom map (also see Table 1). B, summarized results of DNA sequence copy-number analysis by FISH in two different cell lines. The vertical axis shows the number of FISH signals achieved with the BAC probes indicated above. The number of signals was truncated at 20 because it was difficult to enumerate them above this level. Lines connect the measurements made for each cell line. The smallest overlapping region (SRO) with maximal amplification in both cell lines is indicated.
cIAP1 amplification in esophageal squamous cell carcinoma

Results

Definition of the 11q21-q23 Amplicon by FISH. In our previous CGH analysis, we had detected a high-level gain of copy number on 11q21-q23 in 2 of the 29 ESC cell lines examined (KYSE170 and 2270; Ref. 7). This region was clearly distinguished from 11q13, a marker chromosome (Figs. 1A and 2). By contrast, no HSR pattern was observed in either KYSE170 or 2270 lines. In both primary tumors, from which KYSE 170 and 2270 were derived, gene amplification, resulting in overproduction of this protein, had already occurred in the primary tumors, from which KYSE 170 and 2270 were derived. Resolution of ESC Cell Lines with Amplified cIAP1. Overexpression of cIAP1 was observed not only at the mRNA level but at the protein level as well. FISH experiments clearly showed expression of cIAP1 in the cytoplasm of KYSE170 and 2270 cells, the two ESC lines in which concomitant amplification with overexpression of cIAP1 had been detected (Fig. 3C). Cells lines without amplification of cIAP1 showed a considerably lesser degree of cytoplasmic staining for this molecule, in accord with the results of Northern blotting (Fig. 3C).

Next, we performed IHC analysis of cIAP1 using tissue sections of the primary ESC tumors from which the KYSE series of ESC cell lines had been established. As shown in Fig. 3D, moderate to strong staining of cIAP1 was clearly observed in >10% of cancer cells but not in normal epithelial or stromal cells in parent tumors of the KYSE 170 and 2270 lines. In both primary tumors, most immunoreactions occurred in the cytoplasm of cancer cells, at the frontier of stromal invasion. The cIAP1-immunopositive carcinoma cells were usually pleomorphic; they infiltrated into the stroma as single cells or in the form of small nests or strands. In the primary tumor of KYSE2270, strong cIAP1 staining was predominant at the periphery of the small nests (Fig. 3D, right panel). By contrast, we detected no or weak staining of cIAP1 in primary ESC tumors of KYSE cell lines without 11q22 amplification or in breast tumors used as controls (data not shown). These results strongly suggest that amplification of the cIAP1 gene, resulting in overproduction of this protein, had already occurred in the primary tumors, from which KYSE 170 and 2270 were derived.

Resistance of ESC Cell Lines with Amplified cIAP1 to Drug-induced Apoptosis. Because cIAP1 is a member of the IAP family of proteins, and because some IAPs are thought to be involved in carcinogenesis through their antiapoptotic activity (19), we investigated whether the two ESC cell lines with amplification of cIAP1 were resistant to apoptotic stimuli. As shown in Fig. 4A, both KYSE 170 and 2270 exhibited resistance to cDDP and CPT as compared with control cell lines (KYSE200 and 960) in which cIAP1 was not overexpressed. The resistance of KYSE170 and 2270 cells to these anticancer drugs may reflect resistance to chemotherapeutic agent-induced apoptosis, because 10 μg/ml cDDP or CPT induced remark-

Sensitivity of ESC Cell Lines to cDDP and CPT. Next, we performed colorimetric assays using WST-8. For nuclear staining, cells were plated onto glass coverslips and incubated with or without 10 μg/ml cDDP or CPT for 24 h. DNA was extracted from washed cells with the Quick Apoptosis DNA Ladder Detection Kit (Medical & Biological Laboratories, Nagoya, Japan), separated through a 2% agarose gel, and visualized after staining with ethidium bromide.
**cIAP1 Amplification in Esophageal Squamous Cell Carcinoma**

In KYSE170 (data not shown) and 2270 cells, however, few apoptotic cells and little fragmented DNA were observed after the same treatment. The same results were obtained with CPT (data not shown).

**Amplification of cIAP1 in Primary Tumors.** Because cIAP1 seems to be a target for amplification at 11q22, we examined 42 primary ESC tumors that were unrelated to the cell lines to determine whether amplification of cIAP1 had occurred in any of them. By Southern- or dot-blot analysis, an increased signal of the cIAP1 gene was detected in 4 of the 42 tumors examined (9.5%; Fig. 5).

**Discussion**

The 11q22 amplicon we delineate in this study is distinct from the one at 11q13 that has been recognized as commonly amplified in ESCs and other types of tumors (20, 21). Amplification around 11q22 also has been demonstrated by other CGH experiments in a wide variety of human cancers, including ESC, though infrequently (5, 7–12). Primary (9) and metastatic renal-cell carcinomas with sarcomatoid changes (10) sometimes exhibit this alteration. Therefore, the 11q22 region may harbor one or more genes that are activated by amplification and might be associated with progression and/or specific tumor phenotypes. However, neither defined mapping nor screening of putative target genes for the 11q21-q23 amplification has been carried out. This is the first report describing experiments to evaluate potential target genes within that amplicon.

As the first step in exploring the 11q21-q23 region for candidate genes, we constructed a map of the amplicon by FISH to define a relatively small chromosomal region that would make a positional search possible. The criterion we used to define the amplicon is that the best candidate tumor-associated genes, which are selected during amplification process, are located at narrow regions of highest copy number (22). Our determination of the SRO using this criterion and two different cell lines helped to narrow even further the region likely to harbor target gene(s). Even after defined mapping, however, many genes must still exist on an amplicon. The common criterion for designating a gene as a putative target is that amplification leads to its overexpression (23, 24). On the basis of that criterion, we used Northern blots to identify transcripts that were consistently overexpressed in two ESC cell lines where the defined region at 11q22 was amplified (KYSE 170 and 2270) and successfully identified cIAP1 as a strong candidate target for this amplification. Amplification of cIAP1 was detected as well in 4 of 42 unrelated primary ESC tumors, indicating that this genetic alteration is not cell line specific.

The cIAP1 gene product, designated variously as HIAP2, AIP1, MIHH, or BIRC2, was originally identified as a protein recruited to the cytosolic domain of p80 tumor necrosis factor II via its association with tumor necrosis factor-associated factors-1 and -2 (25). cIAP1 protein, like cIAP2 and XIAP in the same subfamily of IAPs, contains three baculovirus IAP repeat domains in the NH2-terminal region and a RING (real interesting new gene) finger domain close to the COOH terminus. Ectopic expression of cIAP1 in mammalian cells can inhibit apoptosis induced by serum deprivation or by a variety of stimuli (19, 26). Consistent with those published observations, our ESC cell lines showing amplification of cIAP1 were resistant to apoptosis induced by chemotherapeutic agents. Our preliminary study demonstrated that those cell lines with amplification of cIAP1 were also resistant to apoptosis induced by radiation, suggesting that overexpressed cIAP1 inhibits apoptosis, regardless of the type of apoptosis-inducing stimulus. Although the mechanism by which cIAP1 suppresses apoptosis is still debated, several studies have provided insights into the biochemical functions of this intriguing protein (19). The central mech-

---

**Table 1**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Probe</th>
<th>Amplified</th>
<th>KYSE170</th>
<th>KYSE2270</th>
</tr>
</thead>
<tbody>
<tr>
<td>cIAP1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMP10</td>
<td>MMP10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMP13</td>
<td>MMP13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATM</td>
<td>ATM</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 3.** A, representative results of Southern-blot analyses using cIAP1, MMP10, MMP13, and ATM probes and a control (GAPDH) in ESC cell lines. DNA from peripheral blood lymphocytes of a healthy donor served as a normal control (N). cIAP1, MMP10, and MMP13 probes were clearly amplified in both KYSE170 and 2270. Note that an increased signal of ATM was also detected in KYSE2270. B, representative results of Northern-blot analyses using cIAP1, MMP10, and MMP13 probes and control (GAPDH) probe in ESC cell lines. Only cIAP1 was consistently overexpressed in the cell lines that showed amplification (KYSE170 and 2270). C, immunofluorescent staining of cIAP1 protein in the same two ESC lines. Cells were counterstained with DAPI. cIAP1 protein was overexpressed in the cytoplasm of KYSE170 and 2270 but not in KYSE200 cells. Negative control, KYSE170 stained with normal rabbit serum. Magnification, ×600. D, immunohistochemical staining of cIAP1 protein in the primary tumors from which KYSE170 and 2270 cell lines had been established. In both tumors, enhanced staining of cIAP1 was observed in the cytoplasm of ESC cells, indicating overexpression of this protein. Magnification, ×200.

---

6 I. Imoto et al., unpublished data.
Fig. 4. A, drug resistance of ESC cell lines having amplification and overexpression of cIAP1. KYSE170, 2270, 200, and 960 were treated with the indicated doses of cDDP (left) or CPT (right). After 48 h, cell viability was determined by colorimetry. Note that KYSE170 and 2270 exhibited resistance to both anticancer drugs, as compared with control lines KYSE200 and 960. Data represent the mean ± SD of three separate experiments, each performed in triplicate. B and C, resistance of KYSE2270 cells to drug-induced apoptosis. Typical nuclear morphological changes (d) and DNA fragmentation (C) occurred in control cell line KYSE200 after 24 h of treatment with 10 μg/ml cDDP. Note the decrease in apoptotic changes in KYSE2270 compared with KYSE200. The same resistance to drug-induced apoptosis was observed in KYSE 170 (data not shown).

Anism appears to be direct inhibition of caspase and procaspase; cIAP1 binds directly to caspases 3 and 7 (27, 28) and also inhibits activation of procaspases 8 and 9 (29, 30). cIAP1 appears to inhibit apoptosis through noncaspase mechanisms as well, e.g., by activation of nuclear factor κB (30) and c-Jun-NH2-terminal kinase (31).

Although evidence for a direct oncogenic role for cIAP1 has yet to emerge, our results indicate that this potent regulator of cell death is likely to play an important role in carcinogenesis. Inhibition of, or increased resistance to, apoptosis is a common property of cancer cells, as it increases their survival time and facilitates their escape from immune surveillance and cytotoxic therapies (19). Therefore, a constitutive activation of antiapoptotic molecules via genetic or epigenetic mechanisms, including gene amplification, may well be involved in carcinogenesis. In follicular and diffuse large B-cell types of non-Hodgkin’s lymphoma, e.g., overexpression of BCL2 through amplification or translocation appears to be associated with progression of the disease (32, 33). Moreover, survivin, another member of the IAP family that is not expressed in normally differentiated tissues, is specifically overexpressed in some cancers (34). Tamm et al. (35) reported that cIAP1 was expressed in most of the cancer cell lines they tested (a panel of 60 human cancer cell lines maintained by the National Cancer Institute), and its expression level was correlated with resistance to several anticancer drugs. Those results and our present findings encourage additional investigation of the functional role of cIAP1 in the genesis of various types of cancer, including ESC, as well as its prognostic relevance.

Our immunocytochemical study using ESC cell lines clearly showed that the amplification mechanism activated cIAP1 and led to overproduction of its product. Moreover, our immunohistochemical study of the archived primary tumors from which those lines had been established indicated that activation of cIAP1 via gene amplification had already occurred in vivo. We infer that activated cIAP1 might confer malignant phenotypes, including invasiveness, metastasis, and drug resistance. The cIAP1-immunopositive cancer cells were observed at the frontier of stromal invasion, and they proliferated into the stroma as single cells or in the form of small nests or strands. These findings suggest that increased immunoreactivity of cIAP1 may reflect a highly invasive potential of ESC cells. Ono et al. (36) observed a similar pattern of immunohistochemical staining for laminin-5 α2 chain in squamous cell carcinomas of the tongue. Their analysis of 67 such tumors demonstrated that strong cytoplasmic localization of the laminin-5 α2 chain was significantly associated with poor prognosis for patients with squamous cell carcinomas of the tongue (36). Accordingly, it will be important to determine the clinicopathological significance of cIAP1 expression in squamous cell carcinomas arising in other organs as well as the esophagus.

Of the 12 transcripts we screened, 11 were excluded as candidates because they were not detectably or consistently expressed in the panel of ESC cell lines we examined. However, of the excluded candidates, cIAP2, which encodes another member of the IAP family, has been identified as a target gene at the breakpoint of a translocation observed often in MALT-type lymphomas (37–39). In MALT lymphomas, cIAP2 is fused to MALT1, and the chimeric protein may be involved in enhanced resistance to apoptosis, although its actual function remains unknown. However, cIAP2 was not overexpressed in any of cell lines we tested, including the two lines having 11q22 amplification. MMP-10 (stromelysin-2) and MMP-13 (collagenase-3) were each highly expressed in only one (KYSE2270) of those two cell lines, although MMP-10 and MMP-13 are often overexpressed in tumor cells, and that feature is correlated with tumor invasion and

![Fig. 5](image_url) Representative results of Southern-blot analysis of cIAP1 and control (GAPDH) in primary ESC tumors. Cases 1 and 6 showed strongly amplified signals with cIAP1. N, normal control from peripheral blood leukocytes of a healthy donor.
aggressiveness, respectively (40, 41). Expression of MMP-10 and/or MMP-13 may be inhibited in KYSE170 by some mechanism, possibly epigenetic. Thus, additional functional and biochemical studies might be needed to absolutely exclude these two genes as amplification targets.

References


\( \text{IAP1 AMPLIFICATION IN ESOPHAGEAL SQUAMOUS CELL CARCINOMA} \)
Identification of cIAP1 As a Candidate Target Gene within an Amplicon at 11q22 in Esophageal Squamous Cell Carcinomas

Issei Imoto, Zeng-Quan Yang, Atiphan Pimkhaokham, et al.


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/61/18/6629

Cited articles
This article cites 41 articles, 16 of which you can access for free at:
http://cancerres.aacrjournals.org/content/61/18/6629.full.html#ref-list-1

Citing articles
This article has been cited by 38 HighWire-hosted articles. Access the articles at:
/content/61/18/6629.full.html#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.