Aberrant L1 Cell Adhesion Molecule Affects Tumor Behavior and Chemosensitivity in Anaplastic Thyroid Carcinoma

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Abstract

Purpose: Anaplastic thyroid carcinoma (ATC) is one of the most invasive human cancers and has a poor prognosis. Molecular targets of ATC that determine its highly aggressive nature remain unidentified. This study investigated L1 cell adhesion molecule (L1CAM) expression and its role in tumorigenesis of ATCs.

Experimental Design: Expression of L1CAM in thyroid cancer was evaluated by immunohistochemical analyses of tumor samples from patients with thyroid cancer. We investigated the role of L1CAM in proliferation, migration, invasion, and chemoresistance using short hairpin RNA (shRNA) knockdown experiments in human ATC cell lines. Finally, we evaluated the role of L1CAM on tumorigenesis with ATC xenograft assay in a nude mouse model.

Results: L1CAM expression was not detectable in normal follicular epithelial cells of the thyroid or in differentiated thyroid carcinoma. In contrast, analysis of ATC samples showed specifically higher expression of L1CAM in the invasive area of the tumor. Specific knockdown of L1CAM in the ATC cell lines, FRO and 8505C, caused a significant decrease in the proliferative, migratory, and invasive capabilities of the cells. Suppression of L1CAM expression in ATC cell lines increased chemosensitivity to gemcitabine or paclitaxel. Finally, in an ATC xenograft model, depletion of L1CAM markedly reduced tumor growth and increased the survival of tumor-bearing mice.

Conclusions: We report that L1CAM is highly expressed in the samples taken from patients with ATCs. L1CAM plays an important role in determining tumor behavior and chemosensitivity in cell lines derived from ATCs. Therefore, we suggest that L1CAM may be an important therapeutic target in patients with ATCs.

Clin Cancer Res; 18(11); 1–8. ©2012 AACR.

Introduction

Anaplastic thyroid carcinoma (ATC) is the most aggressive and invasive type of human thyroid cancer with a median survival of 4 to 6 months. Recent studies have shown that the accumulation of multiple genetic mutations in various genes, such as RAS (1), BRAF (2), TP53 (3), β-catenin (4), PTEN (5), and PIK3CA (6), contributes to ATC tumorigenesis. However, the molecular targets of these genetic events in determining the clinical phenotype and therapeutic potential have not been fully addressed.

L1 cell adhesion molecule (L1CAM) is a member of the immunoglobulin superfamily of cell adhesion molecules (7). It is expressed in developing neuronal cells, renal epithelial cells, hematopoietic cells, endothelial cells, and intestinal crypt cells (8–10). However, the physiologic function of L1CAM in these cells remains unclear. Recent clinical observations have shown that L1CAM expression correlates with tumor progression and metastasis in ovarian carcinoma (11) and colorectal carcinoma (12). The mechanistic involvement of L1CAM in tumor progression was partially explained through the heterophilic interaction between L1CAM and integrins (13, 14). In addition, an
**Translational Relevance**

Anaplastic thyroid carcinoma (ATC) is a highly invasive human cancer that is unresponsive to conventional therapies and has a high mortality rate. Thus, it is important to identify the molecular targets that determine the highly aggressive nature of ATCs. Here, we report that tumors from patients with ATCs have aberrant L1 cell adhesion molecule (L1CAM) expression in the invasive area of the tumor. L1CAM plays an important role in the tumor progression of ATC by enhancing cell proliferation, migration, invasion, and chemoresistance. In addition, we show that the knockdown of L1CAM expression reduces ATC tumor growth in nude mice. We propose that L1CAM plays a critical role in ATC tumorigenesis and chemosensitivity and it may be a promising therapeutic target in patients with ATCs.

**Materials and Methods**

**Patients and tissue specimens**

We retrospectively selected 9 patients with ATCs, 10 patients with nodular hyperplasia, and 200 patients with PTCs who underwent thyroid surgery from January 1998 to December 2008 at the Center for Endocrine Surgery, Chungnam National University Hospital (Daejeon, South Korea). All tumor tissues were reviewed by an experienced pathologist using World Health Organization recommendations on histopathologic typing. All protocols were approved by the Chungnam National University School of Medicine Institutional Review Board.

**Cell culture**

The human anaplastic thyroid carcinoma cell lines FRO (a kind gift from Dr. James A. Fagin, Memorial Sloan-Kettering Cancer Center, New York) and 8505C (DSMZ) were cultured in RPMI-1640 (Invitrogen) with 10% FBS (Hyclone). The human PTC cell lines BCPAP (a kind gift from Dr. Masimmo Santoro, Università di Napoli Federico II, Naples, Italy) and TPC-1 (a kind gift from Dr. Masahide Takahashi, Nagoya University, Nagoya, Japan) were maintained in Dulbecco’s Modified Eagle’s Medium (DMEM; Invitrogen) with 5% FBS. The cell lines FRO, 8505C, and BCPAP harbor a BRAFV600E mutation and TPC-1 cell line has RET/PTC1 rearrangement (16). Primary cultured PTC cells (PCPTC) and primary cultured follicular cells (PCFC) were maintained in 6HT media consisting of Coon modified Ham media/F-12 supplemented with 5% FBS, 1 mlU/ml thyrotropin, 10 μg/ml insulin, 5 μg/ml apotransferrin, 10 nmol/L hydrocortisone, 10 μg/L somatostatin, and 10 μg/L glycyl-histidyl-lysine acetate. SK-OV3 human ovary adenocarcinoma cells were grown in McCoy’s 5A (Invitrogen) with 10% FBS. All cells were maintained in 5% CO₂, 95% relative humidity at 37°C.

**Immunohistochemistry**

Immunohistochemical analysis of L1CAM was conducted with the EnVision-HP Detection System (DakoCytomation) and purified A10-A3, a murine monoclonal antibody against L1CAM (17). All procedures were carried out at room temperature except for incubation of tissue sections with A10-A3, which was conducted at 4°C. Briefly, 4-μm thick sections were cut from tumor tissue blocks, mounted on slides, and dried for 1 to 2 hours at 56°C. The sections were deparaffinized in xylene and rehydrated in graded alcohol. After antigen retrieval in a pressure cooker with Target Retrieval Solution (DakoCytomation; s1699) at full power for 4 minutes, tissue sections were treated with 3% hydrogen peroxide for 10 minutes to block endogenous peroxidases. Sections were incubated overnight with A10-A3 (80 ng/mL) diluted with the Background Reducing Diluent (DakoCytomation; s3022) in a humid chamber at 4°C. Slides were then incubated with the EnVision reagent for 30 minutes followed by diaminobenzidine chromogen for 5 minutes, counterstained with Mayer’s hematoxylin, and mounted. Mouse IgG1 excluding the primary antibody was used as a negative control, and peripheral nerve bundles present in sections served as an internal positive control. Specimens were considered immune-positive for L1CAM when more than 5% of the tumor cells had clear evidence of L1CAM immunostaining as described previously (18).

**Assessment of immunohistochemical staining**

L1CAM expression was semiquantitatively assessed by the immunoreactive scoring (IRS) system. The IRS was based on both the intensity (scored on a 0–3 scale, where 0, no staining; 1, weak staining; 2, moderate staining; and 3, strong staining) and the extent of staining (percentage of positive tumor cells). The staining extent was scored on a 0 to 1 scale, where 0, no staining; 0.1, 1% to 9%; 0.5, 10% to 49%; and 1, 50% to 100%. A final semiquantitative H score, ranging from 0 to 3, was obtained by multiplying both scores.

**L1CAM targeting with short hairpin RNA**

Knockdown of L1CAM was achieved by lentiviral vector–mediated short hairpin RNA (shRNA) interference with...
MISSION shRNA system (Sigma-Aldrich). To select a functional shRNA vector against L1CAM in ATC cell lines, 4 different L1CAM-targeting shRNA vectors and one nontargeting control shRNA vector with scrambled shRNA (5'-CTCTAAGGTTAAGTGCACCTGCCTCAGGAGGCGAC- TTACACCTTACG-3') were introduced into HEK293T cells with packaging vectors using Lipofectamine (Invitrogen) according to the manufacturer's instructions. After 12 hours, the virus generated in the supernatants of these cells was added to 8505C and FRO cells with 5 μg/mL polybrene. After 24 hours, the media were removed and replaced with fresh media containing 1.2 μg/mL puromycin. Puromycin-resistant clones of these were selected after culture for 1 week in the presence of puromycin. To confirm knockdown of L1CAM, the 4 different shRNA clones were evaluated by reverse transcriptase PCR and immunoblotting. From these, we selected a highly functional L1CAM-targeting shRNA (5'-GCGAATGCCTACATCTACGTTCTCGAGAACGTAGAT-GTAGGCATTGGC-3') and used it for all further experiments. Three different clones expressing the functional L1CAM-targeting shRNA were used in the same experiment.

Cell proliferation, migration, invasion, and survival assays
Cells (1.0 × 10^5 cells/mL) were seeded in 6-well plates in 2 mL of media containing 2% FBS. After 72 hours, viable cells were counted in a cell counter (Innovatis AG). Migration and invasion were measured by the Transwell System (Corning Costar) with 6.5-mm diameter polycarbonate filters (8-μm pore size). Briefly, the lower surface of the filter was coated with 10 μg gelatin for the migration assay and the upper surface was coated with 25 μg reconstituted basement membrane substance (Matrigel; BD Biosciences) for the invasion assay. Fresh RPMI-1640 media containing 3% FBS were placed in the lower wells. Cells were incubated for 24 hours in RPMI-1640 media containing 1% FBS, trypsinized, and suspended at a final concentration of 1.0 × 10^6 cells/mL in media containing 1% FBS. Next, 100 μL of the cell suspension was loaded into each of the upper wells and the chamber was incubated at 37°C for 6 hours (migration) or 18 hours (invasion). Cells were fixed and stained with hematoxylin and eosin. Nonmigrating cells on the upper surface of the filter were removed by wiping with a cotton swab. Chemotaxis was quantified by counting the number of surviving mice was determined by monitoring tumor growth–related events (tumor size > 2,000 mm^3) for 30 days.

Statistical analyses
Comparisons of average means were carried with Mann–Whitney U test. Survival was plotted against time after injection (Kaplan–Meier survival curve) and compared by a log-rank test analysis. All reported P values were 2-sided and analyses were conducted with SPSS Version 18.0 for Windows.

Results
L1CAM is highly expressed in ATC
We first examined L1CAM expression in specimens from patients with well-differentiated PTCs and nodular hyperplasia. Immunohistochemical analysis using the L1CAM monoclonal antibody A10-A3 (17) was conducted. Our results show that well-differentiated PTCs and nodular hyperplasia do not express L1CAM (Fig. 1A). However, all cases (6 females and 3 males) of ATC tumor samples exhibited significant L1CAM expression, albeit with varying levels, as shown in Table 1. Of these ATC samples, 7 (cases 1 through 7) showed relatively strong L1CAM expression than in cases 8 and 9. We analyzed the correlation between L1CAM expression and clinicopathologic factors that could affect tumor aggressiveness in patients with ATCs. Eight of these patients were more than 60 years of age and had a large tumor diameter. In addition, their tumors had metastasized into adjacent organs or tissues including muscle, trachea, jugular vein, esophagus, or recurrent laryngeal nerve. Distinct metastases were also observed in bone (case 1) and lung (cases 2 and 9). Case 8 had a relatively small sized (2.5 cm) tumor mass with minimal tumor invasion. L1CAM expression in samples from these 9 patients was assessed semiquantitatively using the IRS system. The IRS is based on both the intensity and extent of staining, as described in the Materials and Methods. The calculated L1CAM expression score was greater than 1.5 in cases 1 through 7 and 0.3 or less in cases 8 and 9 (Table 1). These data indicate that the level of L1CAM expression varies among ATC cases and thus may
not be associated with apparent tumor invasion and metastasis.

Interestingly, analyses of L1CAM expression patterns indicated that L1CAM is abundantly expressed in the invasive area (Supplementary Fig. S1). In cases 1 through 3, moderate and high L1CAM expression was observed in the invasive islands (red arrowhead) of ATCs and L1CAM was also found at the invasive fronts (black arrowhead) in cases 7 and 8 (Supplementary Fig. S1). Four representative images are shown in Fig. 1B. Case 1 showed strong membranous L1CAM expression compared with normal follicular structures in the same area and highly expressed L1CAM was also observed at ATC area compared with papillary structure in case 2. Strong L1CAM expression was displayed in case 3, which had a spindle cell–like ATC throughout the section, and a round shaped ATC with L1CAM expression was noted at the invasive area in case 4. Interestingly, case 4 had a small-sized (0.8 cm) PTC with underlying Hashimoto’s thyroiditis at the initial presentation and underwent lobectomy. At this time, the tumor did not express L1CAM but 2 years later, there was a recurrence and the patient was diagnosed as ATC with observed L1CAM expression (Supplementary Fig. S2). Previously, it was reported that 67% (18 of 27) of ATCs expressed cyclin D1 (19) and 55% (12 of 22) expressed mutant p53 (20). Although cyclin D1 and p53 expression was diffusely or focally observed in 6 of the tested ATC samples, there was no correlation with the degree of L1CAM expression (Supplementary Fig. S3 and Table 1). L1CAM was also found to be highly expressed in the ATC cell lines FRO and 8505C, but not in primary cultured follicular cells or the differentiated thyroid cancer cell lines PCPTC, TPC1, or BCPAP (Supplementary Fig. S4), suggesting that L1CAM expression is a specific marker of ATC tumors.

Taken together, these data suggest that although the overall L1CAM expression in ATC is variable and heterogeneous, it is highly expressed in invasive areas of the tumors.

**Table 1.** Clinicopathologic features of the L1CAM-positive patients with ATC

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/sex</th>
<th>Tumor type</th>
<th>L1CAM expression score</th>
<th>Maximal tumor size, cm</th>
<th>Tumor site</th>
<th>Tumor invasion</th>
<th>TNM staging</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>73/F</td>
<td>ATC</td>
<td>1.5</td>
<td>8</td>
<td>Rt.</td>
<td>Carotid sheath, RLN</td>
<td>T4aN1M1</td>
</tr>
<tr>
<td>2</td>
<td>78/M</td>
<td>ATC</td>
<td>1.5</td>
<td>6</td>
<td>Rt. and Lt.</td>
<td>Tr, Ca, Eso, Ly</td>
<td>T4aN1bM1</td>
</tr>
<tr>
<td>3</td>
<td>80/M</td>
<td>ATC</td>
<td>3</td>
<td>6.5</td>
<td>Lt.</td>
<td>Eso, Lt. Jug. v, Ca, Ex</td>
<td>T4aN1bM0</td>
</tr>
<tr>
<td>4</td>
<td>79/M</td>
<td>ATC</td>
<td>3</td>
<td>5</td>
<td>Lt.</td>
<td>Ca, Ex, Ly, Muscle</td>
<td>T4aN1bM0</td>
</tr>
<tr>
<td>5</td>
<td>85/F</td>
<td>ATC</td>
<td>1.5</td>
<td>10</td>
<td>Rt.</td>
<td>Tr, Ca, Eso, Ly</td>
<td>T4aN1M0</td>
</tr>
<tr>
<td>6</td>
<td>60/F</td>
<td>ATC</td>
<td>1.5</td>
<td>5.5</td>
<td>Lt.</td>
<td>Tr, Eso, Muscle</td>
<td>T4aN1M0</td>
</tr>
<tr>
<td>7</td>
<td>61/F</td>
<td>ATC</td>
<td>1.5</td>
<td>7</td>
<td>Rt. and Lt.</td>
<td>Tr, Ca, Ly</td>
<td>T4aN1M0</td>
</tr>
<tr>
<td>8</td>
<td>44/F</td>
<td>ATC</td>
<td>0.3</td>
<td>2.5</td>
<td>Rt. and Lt.</td>
<td>Ca, Ex</td>
<td>T4aN1M0</td>
</tr>
<tr>
<td>9</td>
<td>72/F</td>
<td>ATC</td>
<td>0.1</td>
<td>10</td>
<td>Rt. and Lt.</td>
<td>Muscle, Tr</td>
<td>T4aN1M1</td>
</tr>
</tbody>
</table>

Abbreviations: Ca, thyroid capsule; Eso, esophagus; Ex, extrathyroidal; Jug. v, jugular vein; Lt., left; Ly, lymphovascular; RLN, recurrent laryngeal nerve; Rt., right; Tr, trachea.
L1CAM plays a crucial role in proliferation, motility, and invasion in ATC cell lines

To investigate whether L1CAM plays an important role in cellular activities of ATC, we first generated cell clones with stable knockdown of L1CAM. Specific depletion of L1CAM was accomplished by lentiviral-mediated transduction and expression of sequence-specific shRNA (Fig. 2A) and the effect on ATC cell proliferation was analyzed. As shown in Fig. 2B, suppression of L1CAM resulted in a significant decrease in the growth rate of FRO cells at 48 hours (15% ± 3.4%) and 72 hours (19.2% ± 2.4%; P < 0.01). In Fig. 2C, depletion of L1CAM caused a significant decrease in the growth rate of 8505C cells at 48 hours (43.7% ± 8.3%) and 72 hours (46% ± 3.7%; P < 0.01). L1CAM has been shown to be necessary for motility and invasiveness of several types of tumors (21, 22). Therefore, we determined the effect of L1CAM on the motility and invasiveness of ATC cell lines using the Transwell system (Corning Costar). Stable L1CAM knockdown FRO cells displayed markedly decreased migration (54% ± 9.5%) and invasion (53% ± 17%) compared with control cells (Fig. 3A and C; P < 0.01). L1CAM knockdown 8505C cells
also exhibited significantly diminished migration (47% ± 4%) and invasion (63% ± 12.8%) compared with control cells (Fig. 3B and D; \( P < 0.01 \)), implying that the expression of L1CAM is important for both motility and invasion in thyroid tumors.

**L1CAM expression is associated with chemoresistance in ATC**

Recently, Voigt and colleagues reported that single exposure of certain chemotherapeutic drugs, including paclitaxel, gemcitabine, and vinorelbine, caused relative antitumor activity in ATC cell lines as compared with cisplatin and doxorubicin (23). However, combination therapy of these drugs did not show significant synergistic antitumor activity. This suggests that chemoresistance in ATC might be a result of the limited effectiveness of combination therapies. Interestingly, enhanced L1CAM expression conferred protection from apoptosis as well as chemoresistance in ovarian carcinoma cells (24). Therefore, we examined whether lack of L1CAM expression might contribute to the chemosensitivity of cells after treatment with gemcitabine or paclitaxel. As shown in Fig. 4A, depletion of L1CAM in FRO cells significantly increased cell death after treatment with gemcitabine (40% ± 6.8%) or paclitaxel (36% ± 4.2%) compared with control cells (\( P < 0.01 \)). In Fig. 4B, suppression of L1CAM in 8505C cells had a similar effect on apoptosis after gemcitabine (36% ± 3%) or paclitaxel (43% ± 6.9%) treatment (\( P < 0.01 \)). These data further support the hypothesis that L1CAM expression correlates with responsiveness to drug therapy in tumor cells.

**L1CAM promotes tumor growth in an ATC xenograft model**

Finally, we evaluated the effect of L1CAM on tumorigenesis in vivo. L1CAM-depleted ATC cells were injected into the right flank of nude mice and tumor formation was monitored. As shown in Fig. 5A and B, a significant delay in tumor growth was observed in mouse xenografts with the L1CAM-depleted cells compared with xenografts of cells transfected with control shRNA. At 19 days after injection, the average tumor volume in mice injected with control shRNA cells was 1,806.1 ± 71 mm³ compared with 731.3 ± 114 mm³ in mice injected with L1CAM shRNA cells. Thus, a remarkable decrease in tumor volume of 60% was achieved (\( P < 0.01 \)). The survival advantage conferred by L1CAM depletion was statistically significant when compared with the control group (\( P < 0.01 \) vs. control shRNA).
group; Fig. 5C). These results clearly suggest that L1CAM has a strong potential to promote the growth and tumorigenicity of ATCs.

Discussion

Thyroid carcinomas are the most common cancer of the endocrine system. Although the majority of thyroid tumors are well-differentiated papillary and follicular thyroid carcinomas with a relatively good long-term prognosis, ATCs are usually fatal. There is a debate about the origin of ATC and whether they originate de novo or from preexisting differentiated carcinoma (20). More importantly, the paucity of specific molecular markers that are useful for diagnosis or therapeutic targets restricts the effective management of ATC. The adhesion molecule L1CAM is highly expressed in a subset of human cancers and was reported to participate in tumor progression (25). The present study showed aberrant L1CAM expression at the infiltrative areas of ATC, whereas L1CAM expression was not detected in nodular hyperplasia and PTC tumors (Fig. 1A and Supplementary Fig. S1). Consistently, strong L1CAM expression was also detected in ATC cell lines but not in normal thyroid follicular cells or well-differentiated thyroid carcinoma cell lines (Supplementary Fig. S4). These data suggest that detectable L1CAM expression is specific to ATC tumors and cell lines and not to thyroid cells in general.

It has been estimated that approximately 10% of patients with colorectal cancer and 40% of patients with extrahepatic cholangiocarcinoma have positive L1CAM expression (12, 17, 26). In addition, L1CAM was expressed in 46% of clear cell renal cell carcinomas and in 28% of papillary renal cell carcinomas (27). In contrast to the relatively low prevalence of L1CAM expression in these cancers, we found that all tested ATC tumors had aberrant L1CAM expression. To evaluate the role of L1CAM, we carried out experiments with L1CAM knocked down in vitro and in vivo. Stable depletion of L1CAM in ATC cell lines significantly reduced the invasive phenotype of the cells. In nude mice with L1CAM-depleted ATC xenografts, we observed distinctive antitumor effects. Interestingly, we found that stable L1CAM knockdown ATC cells had greater sensitivity to gemcitabine or paclitaxel treatment than control ATC cells. These results imply that L1CAM expression is important for tumor progression and the chemoresistant mechanism of ATCs.

Although ATCs may appear de novo in most cases, it can also develop from preexisting, well-differentiated thyroid tumors. In fact, previous studies reported transition zones from differentiated thyroid carcinoma to ATC in the same tumor tissue as well as tiny foci of differentiated thyroid carcinoma within ATCs (28, 29). We also observed these transition zones in case 2, which exhibited moderate L1CAM expression in ATC areas compared with focal L1CAM expression in adjacent papillary structure (Supplementary Fig. S1). In one particular case, the initial diagnosis was PTC without L1CAM expression, but 2 years later, the recurred mass was diagnosed as ATCs with observed L1CAM expression (Supplementary Fig. S2). Although we do not provide direct evidence that L1CAM is responsible for transformation of PTCs to ATCs, these results suggest that aberrant L1CAM expression may appear during ATC transformation.

The location of L1CAM in the cellular membrane makes it a possible diagnostic marker or therapeutic target in patients with ATCs. An antibody targeted to L1CAM was recently reported to reduce cell proliferation in nude mice seeded with ovarian carcinoma cells (30, 31). Moreover, soluble L1CAM was associated with angiogenesis through its interaction with integrins and was discovered in the serum and ascites of patients with ovarian carcinoma (11, 32). These results provide evidence that local recurrence or distant metastasis could be controlled in L1CAM-expressing ATC animal model. L1CAM-targeted therapy may be possible for patients with inoperable or recurrent ATC when combined with concurrent chemotherapy and radiation therapy.

In conclusion, we show that L1CAM is highly expressed in ATC tumors and plays an important role in the aggressiveness of ATCs by enhancing proliferation, migration, invasion, and chemoresistance in vitro. In addition, L1CAM-depleted ATC-xenografted nude mice show marked suppression of tumor growth and prolonged survival. Our results support combined targeted therapy of L1CAM with chemotherapy as a new treatment modality for ATC tumors.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions


Grant Support

This research was supported by a grant from Research Initiative Program and Inno-Project of Korea Research Institute of Bioscience and Biotechnology; a grant of the Korean Health technology R&D Project, Ministry of Health & Welfare, Republic of Korea (No A100588); a grant from the National Research Foundation of Korea (2011-0016309) funded by the Korea government (MEST); and a grant from Research Program (2011-0020507) of the Korea National Research Foundation.

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Received October 30, 2011; revised February 29, 2012; accepted March 17, 2012; published OnlineFirst April 3, 2012.

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Clin Cancer Res; 18(11) June 1, 2012 OF7

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Clin Cancer Res  Published OnlineFirst April 3, 2012.

Updated version  Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-11-2757

Supplementary Material  Access the most recent supplemental material at:
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