NAC-1 Controls Cell Growth and Survival by Repressing Transcription of Gadd45GIP1, a Candidate Tumor Suppressor

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Abstract
Cancer mortality and morbidity are primarily related to recurrent tumors, and characterization of recurrence-associated genes should illuminate fundamental properties of tumor progression and provide new therapeutic targets. We have previously identified NAC-1, a member of the BTB/POZ gene family and a transcription repressor, as a gene associated with recurrent ovarian carcinomas after chemotherapy. We further showed that homodimerization of NAC-1 proteins is essential for tumor growth and survival. In this study, we applied serial analysis of gene expression and identified growth arrest and DNA-damage-inducible 45-γ interacting protein (Gadd45GIP1) as one of the downstream genes negatively regulated by NAC-1. NAC-1 knockdown in both SKOV3 and HeLa cells that expressed abundant endogenous NAC-1 induced Gadd45GIP1 expression transcriptionally; on the other hand, engineered expression of NAC-1 in NAC-1–negative RK3E and HEK293 cells suppressed endogenous Gadd45GIP1 expression. In NAC-1–expressing tumor cells, induction of dominant negative NAC-1 conferred a growth-inhibitory effect that can be partially reversed by Gadd45GIP1 knockdown. Induced Gadd45GIP1 expression resulted in growth arrest in SKOV3 and HeLa cells both in vitro and in vivo. In summary, NAC-1 contributes to tumor growth and survival by at least inhibiting Gadd45GIP1 expression, which has a tumor suppressor effect in cancer cells. [Cancer Res 2007;67(17):8058–64]

Introduction
The genes of the BTB/POZ family act as ubiquitous transcription repressors and participate in several cellular functions, including proliferation, apoptosis, transcription control, and cell morphology maintenance (1). The BTB/POZ proteins share an evolutionarily conserved BTB/POZ protein-protein interaction motif at the NH2-terminal that mediates either homodimer or heterodimer formation (1–3). The POZ domain also facilitates the recruitment of corepressor proteins including histone deacetylases (4), SMRT (5), N-CoR (6), mSin3A (6), and BcoR (7). The roles of BTB/POZ proteins in human cancer have been recently revealed because several of the BTB/POZ proteins have been shown to be involved in cancer development, and they include BCL-6 (8, 9), PLZF (promyelocytic leukemia zinc finger; refs. 8, 10), leukemia/lymphoma related factor (LRF)/Pokemon (11, 12), HIC-1 (hypermethylated in cancer-1), and Kaiso (13, 14). For example, BCL-6 translocations and mutations frequently occur in B-cell lymphoma, resulting in constitutive BCL-6 activation that contributes to the development of B-cell lymphoma. Peptide inhibitors that block interaction between the BCL-6 BTB/POZ domain and its co-repressor suppress BCL-6 oncogenic functions in neoplastic B lymphocytes, suggesting a potential of that peptide inhibitor of the BTB/POZ domain may provide a novel therapeutic agent for B-cell lymphoma (9). Besides, LRF directly represses transcription of the tumor suppressor gene ARF, thus enhancing tumor development (11).

Based on analyzing gene expression levels in all 130 deduced human BTB/POZ genes using the serial analysis of gene expression (SAGE) data, we have recently identified NAC-1 as a carcinoma-associated BTB/POZ gene (15). NAC-1 is a transcription repressor and is involved in self-renewal and maintenance of pluripotency in embryonic stem cells (16). In human cancer, our previous study reveals that NAC-1 is significantly overexpressed in several types of carcinomas including ovarian serous carcinomas, the most malignant and common type of ovarian cancer (15). The levels of NAC-1 expression correlate with tumor recurrence in ovarian serous carcinomas, and intense NAC-1 immunoreactivity in primary ovarian tumors predicts early recurrence (15). Based on co-immunoprecipitation and double immunofluorescence assays, we show that NAC-1 proteins homo-oligomerize through the BTB/POZ domain. Induced expression of the NAC-1 mutant containing only the BTB/POZ domain (N130) disrupts NAC-1 bodies, prevents tumor formation, and enhances apoptosis in mouse xenografts. Overexpression of full-length NAC-1 is sufficient to increase tumorigenicity of ovarian surface epithelial cells and NIH3T3 cells in athymic nu/nu mice. Taken together, our previous studies suggest that NAC-1 is a tumor recurrence-associated gene with oncogenic potential, and the interaction between BTB/POZ domains of NAC-1 proteins is essential for tumor cell proliferation and survival in those tumors with NAC-1 overexpression.

To determine the molecular mechanisms underlying how NAC-1 expression contributes to growth and survival in tumor cells that overexpress NAC-1, we used the NAC-1 dominant negative N130 model to identify the differentially expressed genes in cells with and without N130 induction. Based on SAGE, we identified and validated several genes whose expression was up-regulated by N130 protein induction and, thus, was negatively regulated by NAC1 molecules. One of the NAC-1 negatively regulated genes is the growth arrest and DNA-damage-inducible 45-γ interacting protein (Gadd45GIP1), also known as CR6-interacting factor 1 (CRIF1), which has been shown to bind to the Gadd45 family proteins based on glutathione S-transferase pull-down, mammalian
in a 96-well plate using LipofectAMINE. The results were expressed as the difference between the expression vector, pcDNA4/Gadd45GIP1, with an Xpress tag at the NH2-terminal. The Gadd45GIP1 cDNA was prepared from the OVCAR3 cells, amplified by PCR and cloned into a mammalian expression vector, pcDNA4/His-Max C (Invitrogen). The clone was sequenced to ensure a wild-type coding sequence of Gadd45GIP1. pcDNA/Gadd45GIP1 was then amplified by PCR and cloned into the OVCAR3 cells, amplified by PCR and cloned into a mammalian expression vector, pcDNA4/His-Max C (Invitrogen). The clone was sequenced to ensure a wild-type coding sequence of Gadd45GIP1. pcDNA/Gadd45GIP1 was then stably transfected into the RK3E/NAC-1 and HEK293/NAC-1 clones using the Nucleofector II electroporator (Amaxa). Cell growth and apoptosis assays were done as previously described (20).

Small interfering RNA knockdown of NAC-1 and Gadd45GIP1 gene expression. The small interfering RNA (siRNA) that targeted Gadd45GIP1 was GCCGCGCCGGUAACGCCGCAACUGCUU. Control siRNA (off-target control) was purchased from IDT. The sequences of NAC-1 siRNA were previously reported (15). Cells were seeded onto 96 wells and transfected with siRNAs using OligofectAMINE (Invitrogen).

Tumor xenograft in nude mice. To determine if Gadd45GIP1 induction could prevent tumor formation, we injected 3 × 106 SKOV3 and HeLa cells with Gadd45GIP1 inducible constructs into the subcutaneous tissue of nu/nu mice. For controls, doxycyclin (125 µg/mouse) was injected ip.

Identification and validation of NAC-1 regulated genes. To elucidate the mechanisms underlying the effects of NAC-1 in promoting tumor growth and survival, we used the N130 dominant negative system because N130 was a truncated protein of NAC-1 containing only the BTB/POZ domain (amino acids 1–129 from the NH2-terminal), and induction of N130 was shown to be more potent in inactivating NAC-1 than gene knockdown using siRNA (15). In this study, we did long SAGE and compared the gene expression profiles in N130-induced and non-induced HeLa cells. We found that N130 induction affected transcript levels in only a few genes. There were a total of seven genes that were significantly up-regulated (≥3-fold in tag counts) after N130 induction and could be validated (≥2-fold) by quantitative real-time PCR using the same RNA samples that were used to generate long SAGE libraries (Table 1). The up-regulation of the seven genes by N130 could also be observed in SKOV3 ovarian cancer cells after N130 induction based on real-time PCR analysis. As a control, we induced the expression of C250, the deletion mutant of NAC-1 containing the COOH-terminal 250 amino acids of the NAC-1 protein, in HeLa cells but did not observe a significant fold increase (<1.5-fold) in any of the seven genes. The transcript level of Gadd45GIP1 increased as soon as 9 h after N130 induction and sustained a similar level of expression thereafter. In addition, there were three genes showing marginal down-regulation (2- to 3-fold) in N130-induced cells as compared with non-induced controls based on LongSAGE, but none of them could be validated by real-time PCR (<1.5-fold). Among the seven up-regulated genes, Gadd45GIP1 was selected for further study because it had been shown to be a potential gene that suppresses cellular proliferation and participate in the Gadd45 tumor suppressor pathway (17).

Results

NAC-1-dependent Gadd45GIP1 expression. Induction of N130 expression significantly enhanced the Gadd45GIP1 promoter activity (P < 0.001) and elevated the Gadd45GIP1 mRNA level in HeLa cells (Fig. 1A) as well as the Gadd45GIP1 protein level in both HeLa and SKOV3 cells (Fig. 1B). In contrast, C250 induction did not show any significant effect on the expression levels of Gadd45GIP1 because the Gadd45GIP1 transcript level increased to only 1.094-fold based on quantitative real-time PCR. To further show that Gadd45GIP1 expression depends on NAC-1 proteins, we used two independent but complementary approaches. First, we knocked down NAC-1 in HeLa and SKOV3 cells using siRNA and observed a decrease in the NAC-1 transcript level with a concomitant increase in the Gadd45GIP1 level (Fig. 1C and D). Second, we ectopically expressed NAC-1 tagged with V5 in HEK293 and RK3E cells with undetectable NAC-1 expression and analyzed the change in the Gadd45GIP1 expression levels and cell proliferation (Fig. 2A-C). The NAC-1/V5 stable clones showed higher proliferation activity as compared with the vector-transfected clones at low (0.5%) serum concentration. The transcript and protein levels daily to suppress Gadd45GIP1 expression, whereas doxycyclin was not given into the mice to induce gene expression. Tumor volume was measured every other day for 14 days. To determine if Gadd45GIP1 has tumor suppressor effects on established tumors, we injected the same number of SKOV3 and HeLa cells and induced Gadd45GIP1 expression 9 days after subcutaneous tumors had formed. The tumors were monitored for induction based on green fluorescence using a small animal fluorescence imaging device. Tumor volume was measured daily for 9 days after induction, and tumors were prepared for histopathologic examination and immunohistochemistry study using an anti-M30 antibody (Roche).
of Gadd45GIP1 were significantly reduced in NAC-1 clones as compared with the control cells without NAC-1 expression.

**Functional effects of Gadd45GIP1 expression in vitro**. The above findings suggest that Gadd45GIP1 mediates the growth-inhibitory effect of the dominant negative NAC-1, N130, and is one of the downstream genes negatively regulated by NAC-1. To test this hypothesis, we established an inducible (Tet-off) system in HeLa and SKOV3 cells by expressing the Gadd45GIP1 in tumor cells upon removal of doxycyclin. Because the inducible system drove the expression of Gadd45GIP1 as well as EGFP, we were able to determine the efficiency of gene induction by counting the green fluorescent cells. Based on flow cytometry, we found that the induction efficiency in both SKOV3 and HeLa cell lines was high because more than 90% of cells became green fluorescent 24 h after induction. Based on Western blot analysis, expression of Gadd45GIP1 in SKOV3 and HeLa cells was first detected 24 (although weak) and 48 h after induction, respectively (Fig. 34). For both cell lines, induction of Gadd45GIP1 expression significantly suppressed cell growth as evidenced by the insignificant increase of cell number in a time course of the induced group as compared with the non-induced group (Fig. 3D). Similarly, the colony formation was remarkably reduced in the induced group (Fig. 3C), and the percentage of apoptotic cells was increased in the induced SKOV3 and HeLa cells (Fig. 3D). In addition to determining the effects of Gadd45GIP1 in SKOV3 and HeLa, we further extended the above finding to RK3E and HEK293 clones that were engineered to express NAC-1. Constitutive Gadd45GIP1 expression (driven by a cytomegalovirus promoter) significantly reduced the growth rate of NAC-1 clones as compared with the control cells without Gadd45GIP1 expression (Supplementary Fig. S1). The above results strongly suggested that the overexpression of NAC-1 in tumor cells contributed to tumor growth by negatively controlling the expression of Gadd45GIP1. Thus, we further determined if Gadd45GIP1 knockdown could rescue growth suppression conferred by N130. We treated HeLa cells with siRNA targeting Gadd45GIP1, and as shown in the Supplementary Fig. S2, Gadd45GIP1 siRNA partially restored cellular proliferation from N130 induction in HeLa cells, whereas the control siRNA did not show any effects on cell growth.

**Induction of Gadd45GIP1 expression results in tumor suppression in vivo**. Based on the above findings, we determined if Gadd45GIP1 expression had a growth-inhibitory effect in tumor formation and development in vivo. Tumor xenografts from both SKOV3 and HeLa cell lines were established in the nu/nu mouse model. First, we tested if Gadd45GIP1 expression could prevent tumorigenesis by inducing Gadd45GIP1 expression 2 days after s.c. injection of tumor cells. As shown in Fig. 4, induction of Gadd45GIP1 expression almost completely prevented the formation of subcutaneous SKOV3 tumors (Fig. 4A) and HeLa tumors (Fig. 4B). In contrast, the non-induced cells without Gadd45GIP1 expression grew tumors at all injection sites, which progressively enlarged in size. Representative mice bearing the SKOV3 tumors were shown in Fig. 4C. Second, we determined if Gadd45GIP1 could limit tumor growth in established tumors by expressing

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**Table 1. Differentially expressed genes after induction of N130 NAC-1**

<table>
<thead>
<tr>
<th>Gene name</th>
<th>Unigene number</th>
<th>Gene description</th>
<th>Tag number N130+</th>
<th>Tag number N130-</th>
<th>Real-time PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHC1D2</td>
<td>389996</td>
<td>Coiled-coil helix-coiled-coil helix domain</td>
<td>41</td>
<td>17</td>
<td>9.5-fold up</td>
</tr>
<tr>
<td>DUT</td>
<td>527980</td>
<td>Essential enzyme of nucleotide metabolism</td>
<td>13</td>
<td>2</td>
<td>3.3-fold up</td>
</tr>
<tr>
<td>UBE2J2</td>
<td>191987</td>
<td>E2 ubiquitin-conjugating enzyme family</td>
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<td>0</td>
<td>2.1-fold up</td>
</tr>
<tr>
<td>CAPNS1</td>
<td>515371</td>
<td>Calpain families related to oxidative stress</td>
<td>6</td>
<td>0</td>
<td>2.4-fold up</td>
</tr>
<tr>
<td>GADD45GIP1</td>
<td>515164</td>
<td>Growth arrest and DNA-damage-inducible</td>
<td>41</td>
<td>17</td>
<td>9.5-fold up</td>
</tr>
<tr>
<td>COL4A1</td>
<td>17441</td>
<td>Major type IV collagen chain of basement membranes</td>
<td>13</td>
<td>3</td>
<td>2.6-fold up</td>
</tr>
<tr>
<td>TFES</td>
<td>274184</td>
<td>Transcription factor binding to IGHM enhancer 3</td>
<td>5</td>
<td>0</td>
<td>3.9-fold up</td>
</tr>
</tbody>
</table>

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**Figure 1.** Inactivation of NAC-1 up-regulates Gadd45GIP1 expression. A, expression of N130, the dominant negative of NAC-1, enhances the Gadd45GIP1 promoter activity (left) and gene transcript level (right) in HeLa cells as compared with non-induced controls. The assays were done 48 h after N130 induction, and the data are expressed as the fold increase as normalized to the non-induced group. B, Western blots show that N130 expression increases Gadd45GIP1 proteins (arrows, ~28 kDa) in both SKOV3 and HeLa cells. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as the loading control (~37 kDa). C, NAC-1 gene knockdown reduces NAC-1, but increases Gadd45GIP1 protein expression (left) and mRNA expression (right) in HeLa cells. D, NAC-1 gene knockdown reduces NAC-1, but increases Gadd45GIP1 protein expression (left) and mRNA expression (right) in both protein (left) and mRNA (right) levels in SKOV3 cells. The data of siRNA experiments were obtained 72 h after siRNA treatment and were expressed as fold change as compared with control siRNA-treated cells.
Gadd45GIP1 9 days after the tumors were formed (30 ± 3.8 mm³ for SKOV3 tumors and 120 ± 32 mm³ for HeLa tumors; Supplementary Fig. S3). Five days after discontinuation of doxycyclin, induction of Gadd45GIP1 expression was evidenced by green fluorescence in the subcutaneous tumors in which the tumor cells were previously engineered to express both Gadd45GIP1 and EGFP by a bicistronic promoter. As shown in Supplementary Fig. S3, both SKOV3 and HeLa subcutaneous tumors continued growing in control mice (i.p. injection with doxycyclin), whereas the tumors either stopped growing or decreased in size after Gadd45GIP1 induction (i.p. injection with PBS instead of doxycyclin). The tumor size between induced and non-induced groups was statistically significant (P < 0.001) in the end of experiments for both SKOV3 and HeLa cells. Histologic examination of the tumors excised 10 days after Gadd45GIP1 induction revealed extensive apoptosis in tumor cells based on morphology (Supplementary Fig. S3B) and immunoreactivity with the M30 antibody, which recognizes an apoptosis-specific caspase-cleaved cytokeratin epitope (refs. 21, 22; Supplementary Fig. S3C).

**Discussion**

Using LongSAGE as a discovery tool and real-time PCR as a validation method, we identified and validated seven genes that were up-regulated after NAC-1 inactivation by the dominant negative NAC-1 (N130) but were unable to validate any genes that were down-regulated by NAC-1 inactivation, a finding consistent with transcription repressor roles of the BTB/POZ family members (23, 24). The demonstration of Gadd45GIP1 as one of the downstream effectors that are negatively regulated by NAC-1 is of great interest. Gadd45GIP1, also known as CRIF1 (17), interacts with the growth arrest and DNA damage–inducible protein 45 (Gadd45) family, which plays an important role in genomic stability, DNA repair, cell cycle regulation, and apoptosis (25–27). It has been previously reported that Gadd45GIP1 expression is detected in normal tissues, including thyroid, heart, lymph node, trachea, and adrenal glands, and its expression level is lower in neoplastic tissues, including adrenal adenomas and papillary thyroid carcinoma (17). Gadd45GIP1 co-localized with Gadd45 in the nuclei, and recombinant Gadd45GIP1 proteins inhibited histone H1 kinase activity of immunoprecipitated Cdc2/cyclinB1 and Cdk2/cyclinE. The inhibitory effects were synergistic by Gadd45 proteins. In addition, Gadd45GIP1 interacts with the
Orphan nuclear receptor, Nur77, and inhibits its transactivation (28). Biologically, overexpression of Gadd45GIP1 inhibited cellular proliferation in NIH3T3 cells, and Gadd45GIP1 gene knockdown led to the inactivation of the Rb pathway (17).

The evidence to support a direct role of NAC-1 in regulating expression of Gadd45GIP1 in this study came from the findings based on two experimental systems. First, inactivation of NAC-1 either by dominant negative NAC-1 (N130) expression or RNA interference enhanced Gadd45GIP1 promoter activity and gene expression levels. Second, engineered expression of NAC-1 inhibited Gadd45GIP1 expression in cells without detectable NAC-1 expression. In this study, we observed that ectopic expression of Gadd45GIP1 proteins in NAC-1–expressing tumor cells was associated with growth suppression in both in vitro and in vivo systems, a finding consistent with a previous report demonstrating Gadd45GIP1-induced growth inhibition in NIH3T3 cells (17). Furthermore, Gadd45GIP1 gene knockdown could partially rescue NAC-1 dominant negative (N130)–induced growth suppression, suggesting that additional factors other than Gadd45GIP1 are required for NAC1-mediated increase in cell proliferation. The above results suggest that NAC-1 mediates its function in maintaining cell proliferation and survival at least in part through the inhibition of Gadd45GIP1 expression. Although this is the interpretation that we favor, other alternatives should be considered. For example, it is possible that Gadd45GIP1, which was the focus in this study, may not be the only downstream target that is regulated by NAC-1. Our LongSAGE data provide a list of candidate markers (Table 1) for future exploration to determine if additional factors are involved in mediating NAC-1 function.

This report also suggests that the NAC-1–Gadd45GIP1 is involved in a protein network that sustains a survival signal to cancer cells. Figure 5 is a simplified scheme to illustrate that survival signals from two oncogenic pathways converge to one of the molecular hubs, which is the Gadd45/Gadd45GIP1 nuclear factor-κB (NF-κB) is a multifunctional protein, and the NF-κB pathway represents a well-known surviving signal in cancer. For example, inhibition of NF-κB sensitizes ovarian cancer cells to cisplatin and paclitaxel-induced apoptosis (29, 30). Upon activation, NF-κB translocates to nuclei and is associated with c-myc up-regulation, which in turn down-regulates Gadd45 proteins (31–33). Gadd45 interacts with Gadd45GIP1 and up-regulates MKK4 through mitogen-activated protein kinase kinase kinase 4/MTK1 activation (34), and Gadd45 has been shown as a functional tumor suppressor (35). The enhanced MKK4 activity activates the proapoptotic p-c-Jun–N-terminal kinase (JNK)/p38 signaling, which results in growth arrest and apoptosis (32, 36, 37). Therefore, during tumor development, turning off the Gadd45 pathway seems to be critical for cancer cells to survive under cellular stress and to facilitate tumor growth. In this study, we propose that in addition to the established NF-κB–c-myc–Gadd45 pathway, down-regulation of Gadd45GIP1 by NAC-1 overexpression represents another molecular switch to turn off the Gadd45 death signals (Fig. 5). Gadd45GIP1 has been shown to directly bind to all Gadd45 isoforms, and more importantly, the interaction between Gadd45GIP1 and Gadd45 members enhances the Gadd45 function in a cell culture system (17). Therefore, NAC-1 contributes to tumor progression by suppressing Gadd45GIP1 expression, thus inhibiting Gadd45 activity, preventing activation of MKK4 and proapoptotic p38/JNK activity.

It is likely that in the evolution of cancer cell species, tumor cells acquire multiple strategies to inactivate the Gadd45 cell suppressor signaling. In fact, overexpression of NF-κB (29, 30), gene amplification and transcription up-regulation of c-myc (38–40), and Gadd45 promoter methylation (35, 41, 42) have been reported in human cancers, including ovarian cancer cells. Furthermore, our recent study also showed that homozygous deletion and down-regulation of M KK-4 were detected in ovarian carcinomas (43). The above data, together with the results reported in this study,

![Figure 4](image_url)

**Figure 4**. The in vivo effects of Gadd45GIP1 expression in SKOV3 and HeLa xenografts. A, induction of Gadd45GIP1 expression in SKOV3 cancer cells completely prevents tumor formation in all eight nude mice (○), whereas the tumor volumes continue increasing in non-induced control group (●). B, induction of Gadd45GIP1 expression in HeLa cells almost completely prevents tumor formation in eight nude mice (○), whereas the tumor volumes continue increasing in the non-induced control group (●). C, representative mouse from Gadd45GIP1–induced and non-induced group. No visible or palpable tumor can be detected in Gadd45GIP1–induced mouse, whereas a discrete subcutaneous tumor (arrow) is detected in a non-induced control mouse. The photograph was taken 14 d after Gadd45GIP1 induction.
suggest that cancer cells may likely employ at least a dual molecular system to switch off the Gadd45-mediated growth suppression and apoptosis, i.e., the NF-κB/c-myc/Gadd45 pathway and the NAC-1/Gadd45GIP1 pathway. This hypothesis can explain the clinical findings we observed in which NAC-1 is overexpressed in post-chemotherapy-recurrent tumor samples as compared with the primary untreated specimens and also highlights the critical role of inactivating the Gadd45 pathway in tumor development.

Cancer mortality and morbidity are mainly related to recurrent diseases. Because NAC-1 has been shown to be more frequently overexpressed in recurrent chemo-resistant ovarian carcinomas then in the primary untreated counterparts, the findings from the current study may have clinical implications. For example, Gadd45GIP1 expression resulted in the inhibition of cellular proliferation in vitro and suppression of tumor growth in mice. Therefore, Gadd45GIP1 can further be studied as a new therapeutic target in which Gadd45GIP1 can be combined with N130 in treating tumors with NAC-1 overexpression. Targeting NAC-1 and Gadd45GIP1 at the same time may provide a more effective therapeutic approach in human cancer.

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