14-3-3σ, a p53 regulator, suppresses tumor growth of nasopharyngeal carcinoma

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Abstract

The *14-3-3σ* gene product, up-regulated by p53 in response to DNA damage, is involved in cell-cycle checkpoint control and is a human cancer epithelial marker down-regulated in various tumors. However, its role and function have not been established in nasopharyngeal carcinoma (NPC), a tumor of epithelial origin. Recently, we found that 14-3-3σ interacts with p53 in response to DNA damage and stabilizes the expression of p53. In addition, we also showed that overexpression of 14-3-3σ inhibits oncogene-activated tumorigenicity. In the present study, we investigated the tumor-suppressive role of 14-3-3σ in NPC cells. We found that there is a failure to up-regulate 14-3-3σ in response to DNA damage in two NPC cell lines that have p53 mutation. We also found that 14-3-3σ interacted with protein kinase B/Akt and negatively regulated the activity of Akt. Overexpression of 14-3-3σ inhibited NPC cell growth and blocks DNA synthesis. Overexpression of 14-3-3σ also led to inhibition of anchorage-independent growth of NPC cells. In addition, we found that 14-3-3σ sensitized NPC cells to apoptosis induced by the chemotherapeutic agent 2-methoxyestradiol. Overexpression of 14-3-3σ in both NPC cell lines reduced the tumor volume in nude mice, which could have significance for clinical application. These findings provide an insight into the roles of 14-3-3σ in NPC and suggest that approaches that modulate 14-3-3σ activity may be useful in the treatment of NPC. [Mol Cancer Ther 2006;5(2):253–60]

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Introduction

Nasopharyngeal carcinoma (NPC) is a malignancy arising from the epithelial cells lining the nasopharynx (1). It is endemic in southern China and Southeast Asia, with a characteristic of remarkable racial and geographic distribution, and has caused very serious health problem in these areas (1). Etiologic studies indicated that EBV infection, dietary exposure to carcinogens (2), and genetic susceptibility are associated with NPC (3). However, the molecular basis of NPC pathogenesis is not yet well defined. Radiotherapy and chemotherapy are the most common treatment modalities for NPC; however, the patient outcome is not ideal. To develop better treatment approaches, it is important to understand the molecular basis of the development and progression of NPC.

We previously characterized the protein 14-3-3σ (4), which negatively regulates the cell cycle progression by inhibiting the activities of cyclin-dependent kinases (4). Importantly, 14-3-3σ has tumor-suppressive activity and also serves as a target of two important tumor suppressors: p53 (5) and BRCA1 (6). p53 Up-regulates 14-3-3σ to guard genomic stability in response to DNA damage (5). BRCA1 is a coactivator of p53 to induce 14-3-3σ transcription (6). Also, 14-3-3σ interacts with p53 and positively potentiates the activity of p53 (7). Because of 14-3-3σ function in regulating cell cycle and p53, it is conceivable that 14-3-3σ is a potential tumor suppressor and deregulation of 14-3-3σ will have serious effect on tumorigenesis. Importantly, 14-3-3σ, originally a human mammary epithelial-specific marker (HME1; ref. 8), is down-regulated in several types of cancer, including breast cancer (9), gastric cancer (10), hepatocellular carcinoma (11), and lung cancer (12). Overexpression of 14-3-3σ suppresses the anchorage-independent growth of several breast cancer cell lines (4) and inhibits oncogene-activated tumorigenicity (7). These observations suggest that the tumor suppressor function of 14-3-3σ is compromised during tumorigenesis. We are very interested in investigating the role of 14-3-3σ in tumorigenesis of NPC, which is of epithelial origin. Also, little is known about the DNA damage response in NPC. Here, we show that 14-3-3σ is not properly up-regulated in response to DNA damage in NPC. We found that 14-3-3σ can negatively regulate Akt, inhibit cell proliferation, sensitize NPC cells to apoptosis induced by the chemotherapeutic agent 2-methoxyestradiol (2-ME), and can block transformation in two nonisogenic NPC cell lines. Significantly, we also showed that 14-3-3σ overexpression reduces tumorigenicity of NPC cells in nude mice. These results suggest that approaches that modulate the activity of 14-3-3σ may be useful in the treatment of NPC.

Materials and Methods

Cell Culture and Reagents

Two nonisogenic NPC cell lines, CNE1 and CNE2, were obtained from the Zhongshan University in China. CNE1 and CNE2 cells have identical AGA (arginine) to ACA (threonine) changes at codon 280 of p53. These cells were cultured in RPMI 1640 containing 10% fetal bovine serum. A549 cells obtained from American Type Culture Collection (Manassas, VA) were cultured in DMEM containing 10% fetal bovine serum. Ad-HA-14-3-3σ and Ad-Ad-β-gal viruses (5) were produced as previously described (13). Adriamycin and 2-ME were from Sigma (St. Louis, MO).

Western Blot Analysis

Total cell lysates were processed as previously described (14). For the immunoprecipitation assay, the cells were lysed and immunoprecipitated with antihemagglutinin (anti-HA, Babco, Denver, PA) or anti-14-3-3σ from RDI (Flanders, NJ) and immunoblotted with indicated antibodies. Western blot analysis was done with primary antibodies: monoclonal antibodies against HA (12CA5, Babco); antibodies against Akt, phospho-Akt (Ser^{473}) 4E2 from Cell Signaling (Beverly, MA); and antibody against p53 from Oncogene Science (San Diego, CA). Subsequently, membranes were washed and incubated for 0.5 hour at room temperature with peroxidase-conjugated secondary antibodies. Following several washes, membranes were incubated with enhanced chemiluminescence.

3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide Assay, Fluorescence-Activated Cell Sorting Assay, Soft Agar Colony Formation Assay, and Bromodeoxyuridine Incorporation Assay

CNE1 and CNE2 cells were infected with Ad-HA-14-3-3σ [multiplicity of infection (MOI) = 5 or 10] or Ad-β-gal (MOI = 5 or 10) and compared with untreated cells (PBS control) for the assays. These assays were done as previously described (15).

Apoptosis Assays

CNE1 and CNE2 cells were treated with Ad-HA-14-3-3σ (MOI = 5 or 10), Ad-β-gal (MOI = 5 or 10) in DMEM, or combined with apoptotic stimulus (3 or 10 μmol/L 2-ME). After induction of apoptosis, floating and attached cells were harvested 16 hours after the treatment. Cells were lysed at room temperature for 30 minutes and dilutions of these extracts were used for the cell death ELISA, which was done according to the protocol of the manufacturer (Roche Applied Science, Mannheim, Germany).

Tumor Growth in Nude Mice

Female 4- to 5-week-old nude mice (Charles River Laboratories, Wilmington, MA) were divided into three experimental groups, six for each. CNE1 and CNE2 cells were left uninfected (control) or infected with Ad-β-gal (MOI = 5 or 10) or Ad-14-3-3σ (MOI = 5 or 10) for 48 hours. Cells (2×10^6) were harvested and injected s.c. into the

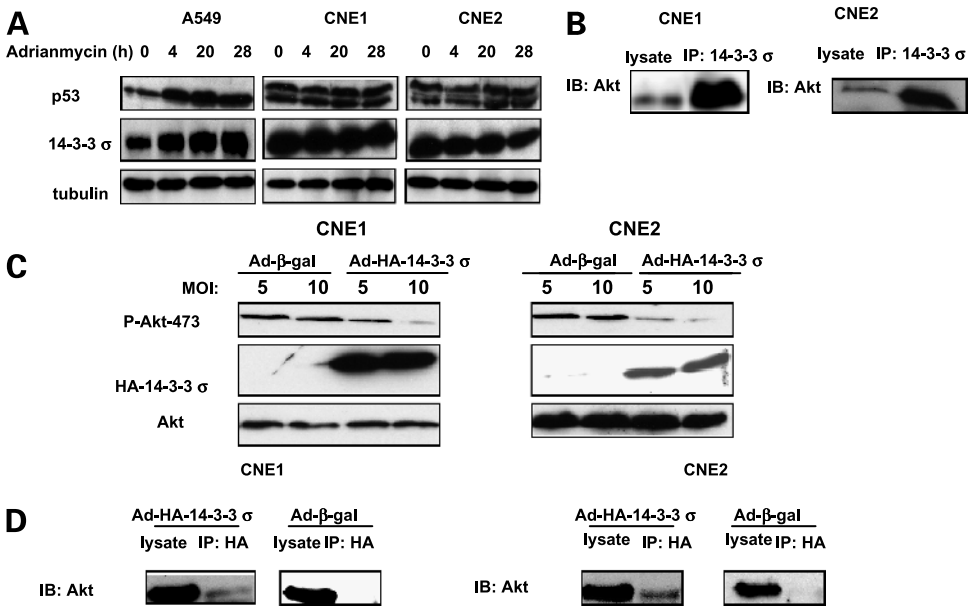

Figure 1. Roles of 14-3-3σ in DNA damage response and Akt inhibition. **A,** 14-3-3σ expression in response to DNA damage. A549, CNE1, and CNE2 cells were treated with 0.2 μg Adriamycin per milliliter for the indicated hours. Equal amounts of cell lysates were immunoblotted with indicated primary antibodies. Tubulin served as a loading control. **B,** interaction of Akt with 14-3-3σ in NPC cells. NPC cell lysates were immunoprecipitated (*IP*) with anti-14-3-3σ, then resolved in SDS-PAGE and immunoblotted with anti-Akt antibody. Cell lysates were immunoblotted (*IB*) with anti-Akt antibody to show the position of Akt. **C,** effects of 14-3-3σ on the phosphorylation of Akt in CNE1 and CNE2 cells. CNE1 and CNE2 cells were infected with Ad-β-gal or Ad-HA-14-3-3σ at the indicated MOIs. Cell extracts were subjected to immunoblot analysis with specific antiphosphorylated Akt at Ser^{473}, anti-HA, or anti-Akt. **D,** interaction of Akt with exogenous14-3-3σ. CNE1 and CNE2 cells were infected with Ad-β-gal or Ad-HA-14-3-3σ for 48 h. Cell lysates were also immunoprecipitated with anti-HA antibody to immunoprecipitate HA-14-3-3σ, resolved in SDS-PAGE, and immunoblotted with antibodies against Akt to observe the association between Akt and HA-14-3-3σ. Cell lysates were immunoblotted with anti-Akt antibody to show the position of Akt.

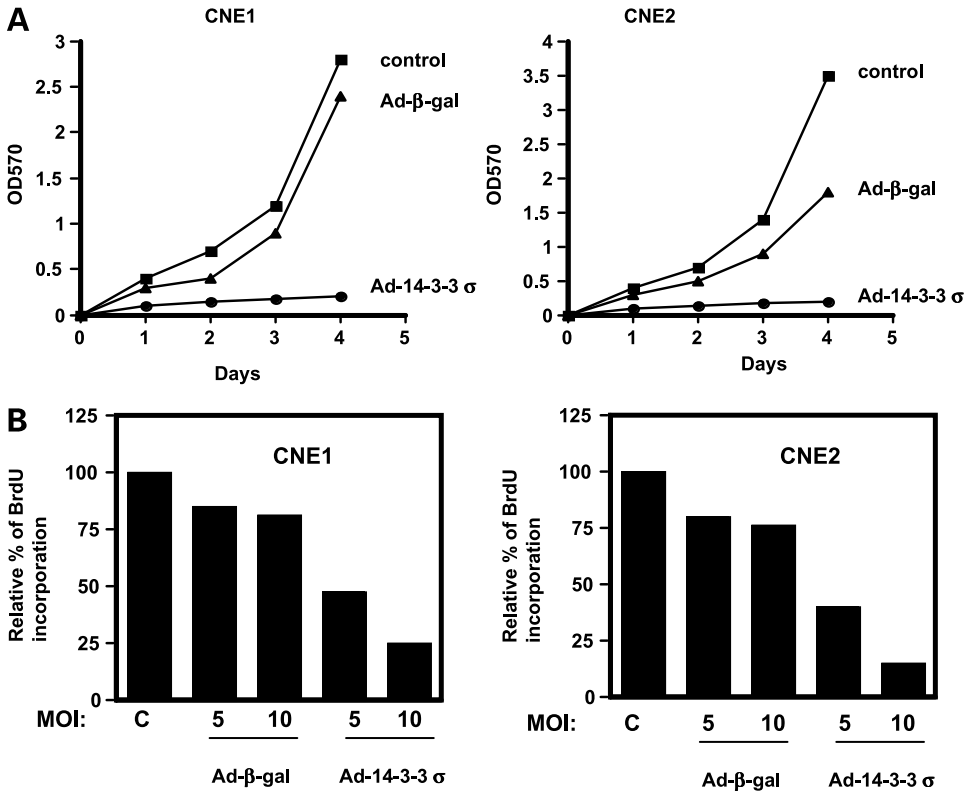

Figure 2. 14-3-3σ inhibits NPC cell growth and blocks cell cycle entry into S phase. **A,** 14-3-3σ overexpression inhibits cell growth of NPC cells. CNE1 and CNE2 cells were left uninfected (*control*) or infected with Ad-β-gal or Ad-14-3-3σ. Cell growth was then estimated by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay every day for a total of 4 d. *Points,* A_{570} reading (*OD570*); *bars,* SD. The absorbance is directly proportional to the number of cells. **B,** 14-3-3σ overexpression blocks NPC cell cycle entry into the S phase. CNE1 and CNE2 cells were left uninfected (*control*) or infected with Ad-β-gal or Ad-14-3-3σ at the indicated MOIs. Incorporation of BrdUrd was examined under a fluorescence microscope using FITC-conjugated anti-BrdUrd. BrdUrd-positive cells were counted in a pool of cells. Three hundred cells were counted for BrdUrd staining in each group of cells. The number of BrdUrd-positive cells from the control group was set as 100%. The relative percentage of BrdUrd-positive cells in cells infected with Ad-β-gal or Ad-14-3-3σ is shown. Data are from a typical experiment conducted in triplicate.

right flank of mice. Tumor volumes were measured as described (15). At the end of experiment, the mice were sacrificed and the tumors were removed for detection of HA-14-3-3σ.

Results

Activation of p53-14-3-3σ Pathway in Response to DNA Damage Is Defective in NPC Cells

Given that 14-3-3σ is an epithelial marker down-regulated in many types of cancer, we were interested in examining the level of 14-3-3σ expression in NPC cells, which are of epithelial origin. We used two nonisogenic NPC cell lines: CNE1 (well differentiated) and CNE2 cells (poorly differentiated). These two NPC cell lines have different p16 expression levels, CNE1 (low) and CNE2 (high), but have identical p53 mutations and similar morphologic features (16). Because 14-3-3σ is up-regulated by p53 in response to DNA damage, we then determined whether this regulation was intact in these two cell lines. We used the topoisomerase inhibitor Adriamycin to trigger DNA damage event. We found that p53 can be stabilized by DNA-damaging agent Adriamycin in lung carcinoma A549 cells, which has wild-type p53 (Fig. 1A). Moreover, 14-3-3σ was up-regulated by p53 following DNA damage in A549 cells. In contrast, there was no change in p53 and 14-3-3σ even 28 hours after treatment with Adriamycin in CNE1 and CNE2 cells that have p53 mutation. As a result, p53-mediated up-regulation of 14-3-3σ was not observed in CNE1 and CNE2 cells, suggesting defective regulation of the p53-14-3-3σ pathway in response to DNA damage.

We recently discovered that overexpression of 14-3-3σ leads to inhibition of Akt activity in the Akt-activated cells,[4] such as Rat1-Akt cells. We then determined whether 14-3-3σ also inhibits Akt activity in NPC cells using adenoviral gene delivery. Because 14-3-3σ physically interacts with Akt to exert its inhibitory activity,[4] we determined whether 14-3-3σ interacts with Akt in NPC cells. We did coimmunoprecipitation experiments and found that endogenous Akt is present in the 14-3-3σ immunoprecipitation complex

[4] H.Y. Yang, et al. DNA damage-induced protein 14-3-3σ inhibits PKB/Akt activation and suppresses Akt-activated cancer, Cancer Research, in press.

(Fig. 1B), indicating that interaction between 14-3-3σ and Akt also exists in NPC cells. We found that Akt is not present in the control IgG immunoprecipitation complex (data not shown), suggesting that the interaction is specific. We then infected CNE1 and CNE2 cells with Ad-β-gal (control) or Ad-14-3-3σ at various MOIs to investigate the effect of 14-3-3σ on Akt. We found that the phosphorylation that affects Akt activation (Akt-p at Ser^{473}) was diminished after adenoviral delivery of 14-3-3σ in both CNE1 and CNE2 cells when compared with cells infected with Ad-β-gal (control; Fig. 1C). These data suggest that overexpression of 14-3-3σ leads to inhibition of Akt activity. We also found that 14-3-3σ interacted with Akt in Ad-14-3-3σ–infected NPC cells (Fig. 1D) by performing coimmunoprecipitation experiments, whereas no such interaction was observed in Ad-β-gal–infected NPC cells. As expected, Akt is not present in the control IgG immunoprecipitation complex (data not shown), suggesting specific interaction. These data suggest that 14-3-3σ can interact with Akt to inhibit the activation of Akt in NPC cells.

14-3-3σ Inhibits Mitogenic Growth of NPC Cells

We previously showed that 14-3-3σ inhibits cyclin-dependent kinase activity, thereby blocking cell cycle progression (4). Given that 14-3-3σ blocked Akt activation in NPC cells (Fig. 1), we assayed whether the inhibitory activity of 14-3-3σ toward cyclin-dependent kinase 2 and Akt can affect the mitogenic growth of NPC cells. CNE1 and CNE2 cells were infected with Ad-β-gal, Ad-14-3-3σ, or left uninfected (control). We measured growth rate as determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay (4) and did a bromodeoxyuridine (BrdUrd) incorporation assay of DNA synthesis. The Ad-14-3-3σ–infected cells exhibited a reduced growth rate (Fig. 2A) as shown by the decreased value of the A_{570} reading. The absorbance is directly proportional to the number of cells. In addition, the Ad-14-3-3σ–infected cells have a decreased BrdUrd-positive population when infected with a high MOI (Fig. 2B) compared with their controls and Ad-β-gal–infected cells, suggesting that high levels of 14-3-3σ expression can efficiently block DNA synthesis in NPC cells.

We also subjected uninfected cells (control) and cells infected with Ad-HA-14-3-3σ or Ad-β-gal to fluorescence-activated cell sorting analysis to investigate cell cycle distribution. CNE1 and CNE2 cells infected with Ad-14-3-3σ had an increased G_2-M population compared with controls and Ad-β-gal–infected cells, suggesting that the expression of 14-3-3σ results in cell cycle arrest in the G_2-M phase (Fig. 3). In addition, Ad-14-3-3σ–infected cells had a higher sub-G_1 population than did control cells or Ad-β-gal–infected cells, indicating that the overexpression of 14-3-3σ can overcome the survival signal in NPC cells to induce apoptosis, as evident in the increased number of sub-G_1 cells (Fig. 3).

14-3-3σ Inhibits Cell Survival and Potentiates Efficacy of 2-ME

Akt has been implicated in the control of cell survival. For example, mice with targeted disruption of the *akt1* gene

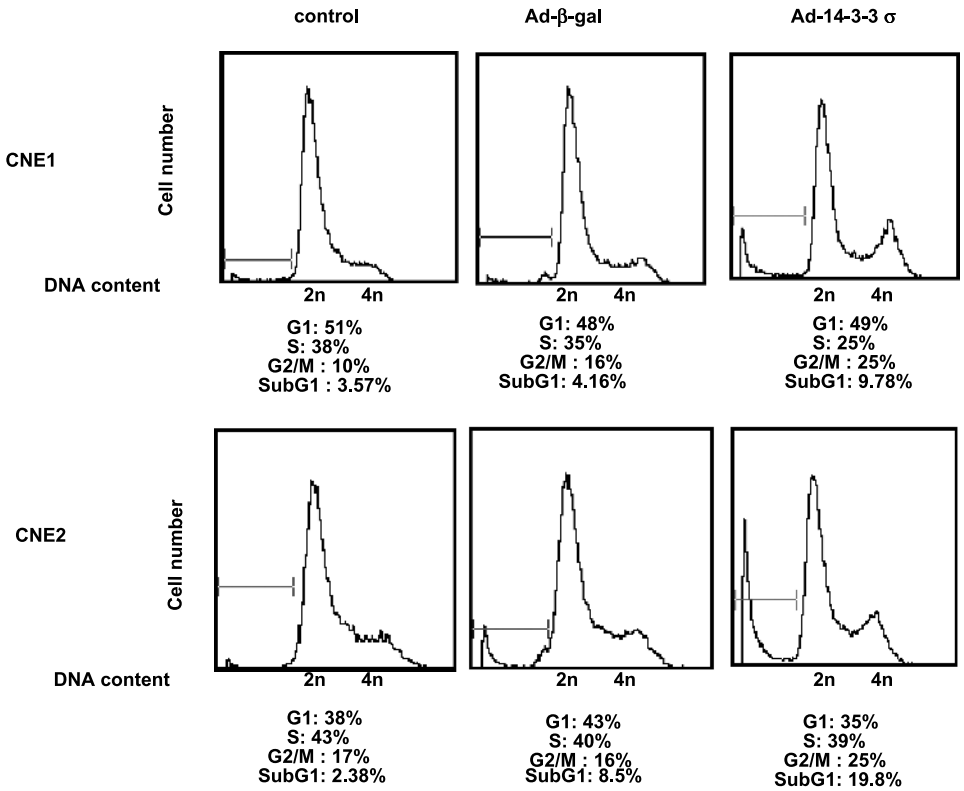

Figure 3. 14-3-3σ Causes G_2-M accumulation of NPC cells. Flow-cytometric analysis was done on CNE1 and CNE2 cells infected with Ad-β-gal, Ad-14-3-3σ (MOI = 10), or left uninfected (control) for 48 h. The percentages of cells in different phases of the cell cycle are shown.

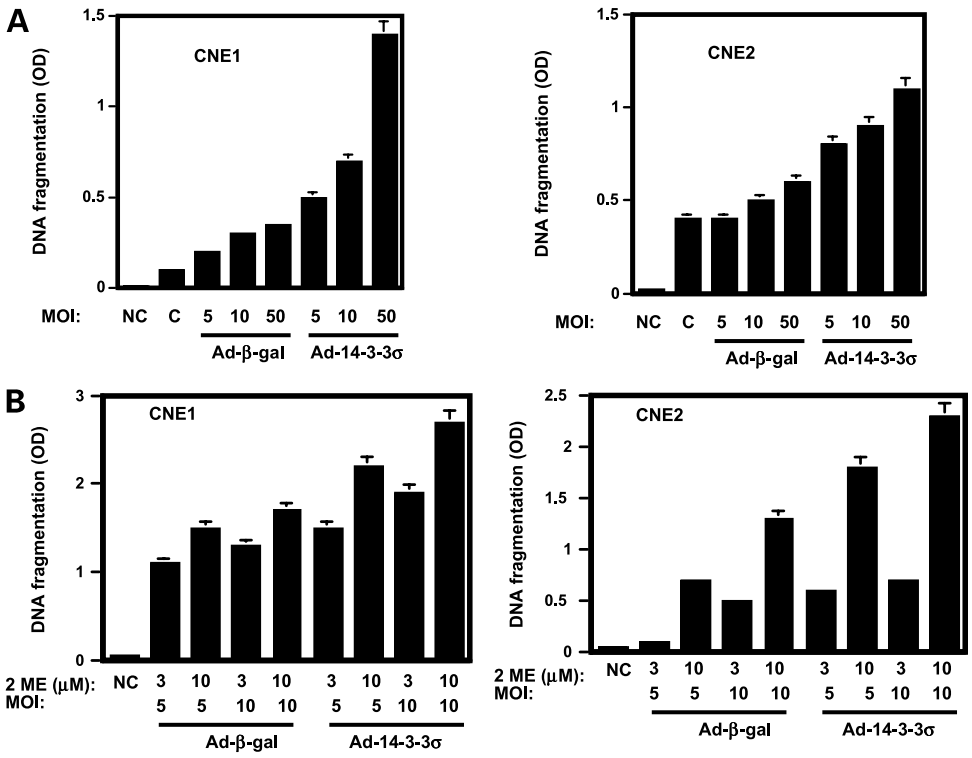

Figure 4. 14-3-3σ Overexpression decreases cell survival and potentiates drug sensitivity in NPC cells. **A,** CNE1 and CNE2 cells were sensitized to apoptosis by adenoviral transduction of 14-3-3σ. CNE1 and CNE2 cells were infected with Ad-14-3-3σ at the indicated MOIs for 48 h or infected with Ad-β-gal at the indicated MOIs. Uninfected cells were used as controls (*C*). Induced apoptosis was determined by measuring DNA fragmentation using a cell death ELISA kit (Roche Applied Science). The results were expressed as the value of A_{405} reading. The absorbance (*OD*) is directly proportional to the number of apoptotic cells. *Columns,* average of three independent experiments; *bars,* SE. ELISA agents were used as negative controls (*NC*). **B,** 14-3-3σ sensitizes NPC cells to chemotherapeutic drug 2-ME-induced apoptosis. CNE1 and CNE2 cells were also treated with 2-ME at the indicated concentrations. Induced apoptosis was determined as described in **A**.

are more sensitive to apoptosis-inducing stimuli (17). Because 14-3-3σ inhibits Akt activity, we next tested whether 14-3-3σ could block cell survival in two NPC cell lines. Cells were left uninfected (control) or infected with Ad-HA-14-3-3σ or Ad-β-gal and subjected to apoptosis assay. We infected the cells with various MOIs to determine whether the 14-3-3σ–induced apoptosis in NPC cells is also dose dependent. We measured apoptosis by quantitating DNA fragmentation. We found that increased MOIs of Ad-14-3-3σ led to 3- to 6-fold increases in DNA fragmentation over that seen in control cells or cells infected with Ad-β-gal (Fig. 4A), indicating that 14-3-3σ overexpression causes apoptosis in NPC cells.

Moreover, we investigated whether 14-3-3σ increased the efficiency of apoptosis induced by 2-ME, a new anticancer agent that inhibits superoxide dismutase and induces apoptosis in cancer cells (18). Significantly, NPC cells treated with 2-ME and Ad-14-3-3σ showed a 2-fold increase in DNA fragmentation over cells treated with 2-ME and Ad-β-gal (Fig. 4B), indicating that 14-3-3σ sensitizes NPC cells to apoptosis induced by 2-ME. Thus, 14-3-3σ promotes apoptosis and potentiated the apoptotic effect of 2-ME in NPC cells.

14-3-3σ Inhibits Transformation and Tumorigenicity of NPC Cells

We next investigated whether 14-3-3σ overexpression affects the transformation phenotype of NPC cells. Because of the transformation phenotype, the NPC cells can grow in soft agar (anchorage-independent growth). Cells were left uninfected (control) or infected with Ad-HA-14-3-3σ or Ad-β-gal and subjected to a soft agar colony formation assay (Fig. 5A). Adenoviral delivery of 14-3-3σ into NPC cells resulted in fewer colonies than control and Ad-β-gal infection (Fig. 5B), demonstrating that the overexpression of 14-3-3σ can suppress the *in vitro* transformation phenotype of NPC cells.

Next, we explored the tumor-suppressive activity of 14-3-3σ in NPC xenograft models. CNE1 or CNE2 cells were left uninfected (control) or infected with Ad-HA-14-3-3σ (MOI = 5 or 10) or Ad-β-gal (MOI = 5 or 10). The cells were then implanted into nude mice. Tumor growth was observed in control mice and Ad-β-gal–treated mice. Remarkably, tumor volume was dramatically decreased in Ad-HA-14-3-3σ–treated mice (Fig. 6A), suggesting that 14-3-3σ inhibits NPC tumorigenicity. As expected, transduced HA-14-3-3σ proteins were present in the small tumors in Ad-HA-14-3-3σ–treated mice but were absent in the larger tumors in control mice and Ad-β-gal–treated mice (Fig. 6B), suggesting that the overexpression of 14-3-3σ is directly involved in inhibiting tumor growth.

Discussion

The molecular basis of the NPC pathogenesis remains poorly defined, which has hindered the development of new treatments. In this study, we found defective regulation of the p53-14-3-3σ pathway in NPC cells, indicating that the important biological activity of 14-3-3σ is compromised in NPC. We showed that 14-3-3σ expression inhibited cell growth and counteracted Akt oncogenic

signaling in NPC cells. We then exploited the tumor-suppressive activity of 14-3-3σ and found that overexpression of 14-3-3σ inhibited tumorigenicity in cancer models. These data suggest that strategic overexpression of 14-3-3σ will be useful in the treatment of NPC.

In NPC cells, we found that p53 protein level fails to be induced in response to DNA damage. However, the amount of p53 was high in CNE1 and CNE2 cells even before DNA damage occurred. It is not clear why p53 is abundant in these two cell lines given that p53 has a short half-life. However, this finding is reminiscent of Sheu et al.'s (19) observation that the p53 protein is overexpressed in NPC. The abundance of p53 in NPC suggests that mutation of the *p53* gene or altered function of the p53 protein contributes to carcinogenesis in NPC. Importantly, both CNE1 and CNE2 cells failed to induce a very important p53 regulator 14-3-3σ in response to DNA damage, indicating that a delicate regulatory pathway is blocked. Given that 14-3-3σ is important to negatively regulate cyclin-dependent kinase (a positive regulator of cell growth; ref. 4) and Akt (a positive regulator of cell survival),[4] this failure to induce 14-3-3σ in response to DNA damage gives NPC cell the mitotic advantage and promotes cell survival.

Because NPC is of epithelial origin and has a high level of expression of the epidermal growth receptor (20), which activates the Akt signaling pathway, Akt could be an important target for NPC therapy. The Akt oncogene is a crucial regulator of a variety of cellular processes, including cell survival and proliferation. The ability of Akt to promote survival is dependent on its kinase activity (17, 21). The inhibition of Akt activation by 14-3-3σ likely affects Ad-14-3-3σ–induced apoptosis in NPC cells. Further, our finding that 14-3-3σ sensitized NPC cells to chemotherapeutic drug–mediated apoptosis is reminiscent of the observation that Akt1−/− mouse embryonic fibroblasts are more susceptible to apoptosis stimuli than are wild-type Akt mouse embryonic fibroblast cells (17). Akt regulates Bad (22, 23), nuclear factor-κB (24), c-Myc (25), Bax (26), forkhead transcription factor (27, 28), cytochrome *c* release (29), and inhibition of Ced3/ICE–like proteases (caspases; ref. 21) to inhibit apoptosis. Also, Akt affects cell cycle progression by regulating the cyclin D protein level (30); by phosphorylating Mdm2 (31), p21 WAF1 (32), and $p27^{Kip1}$ (33–36); or by regulating the forkhead transcription factor FOXO4-p27 pathway (37). Given that 14-3-3σ inhibits Akt kinase activity, 14-3-3σ may be involved in regulating some of these signals. Further investigation of the role of 14-3-3σ in regulating these Akt target molecules may provide important strategies for NPC rational cancer therapy.

The involvement of tumor suppressor genes in NPC cancer has been investigated, including *p53* (19, 38), *p16* (39), *RASSF1A* (40), *RB/p105* (41, 42), and *RB2/p130* (43). NPC has various mutations or deletions in some of these important tumor suppressors. Thus far, *p53* (44), *p16* (16), and *RASSF1A* (45) are able to show their tumor-suppressive activity. In our study, we showed that the tumor-suppressive function of 14-3-3σ is compromised in NPC cells. Using 14-3-3σ adenoviral gene delivery, we found that 14-3-3σ is a powerful tumor suppressor in NPC, suggesting its potential use as an anticancer agent for NPC. Previously, Ad-p16 gene transfer was explored in NPC cancer therapeutic models using CNE1 and CNE2

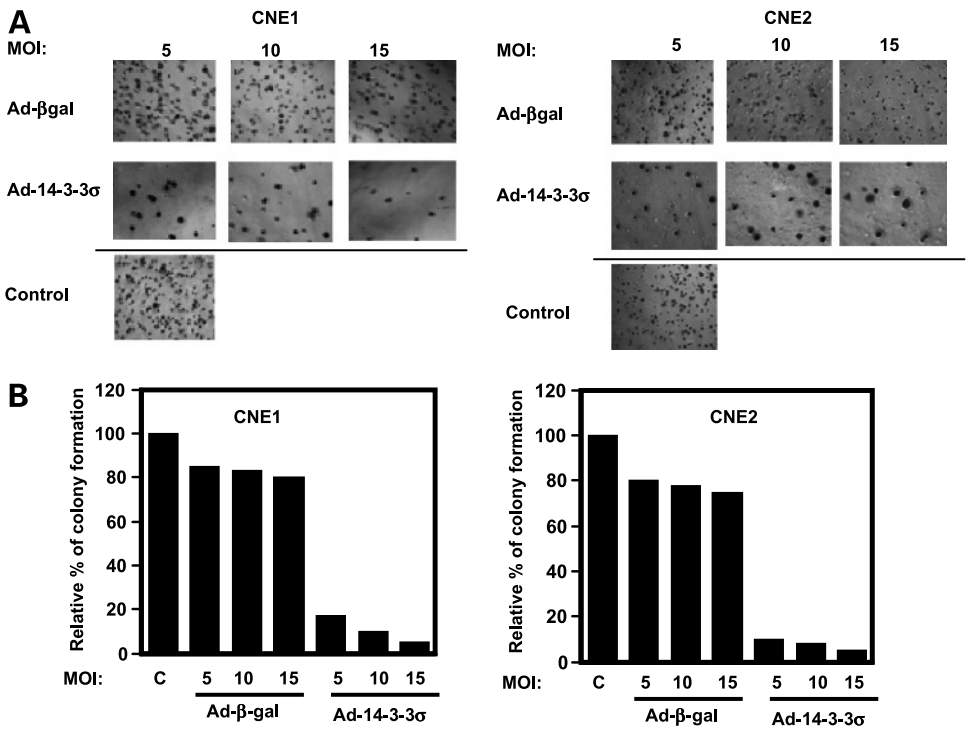

Figure 5. 14-3-3σ Inhibits transformation phenotype of NPC cells. **A,** soft-agar colony formation assay. CNE1 and CNE2 cells were left uninfected (*Control*) or infected with Ad-β-gal or Ad-14-3-3σ at the indicated MOIs. CNE1 and CNE2 cells were then measured for anchorage-independent growth in soft agar. **B,** quantification of colony formation. The relative percentage of colony formation from cells infected with Ad-HA-14-3-3σ or Ad-β-gal is shown. The number of colonies from uninfected cells (control) was set as 100%.

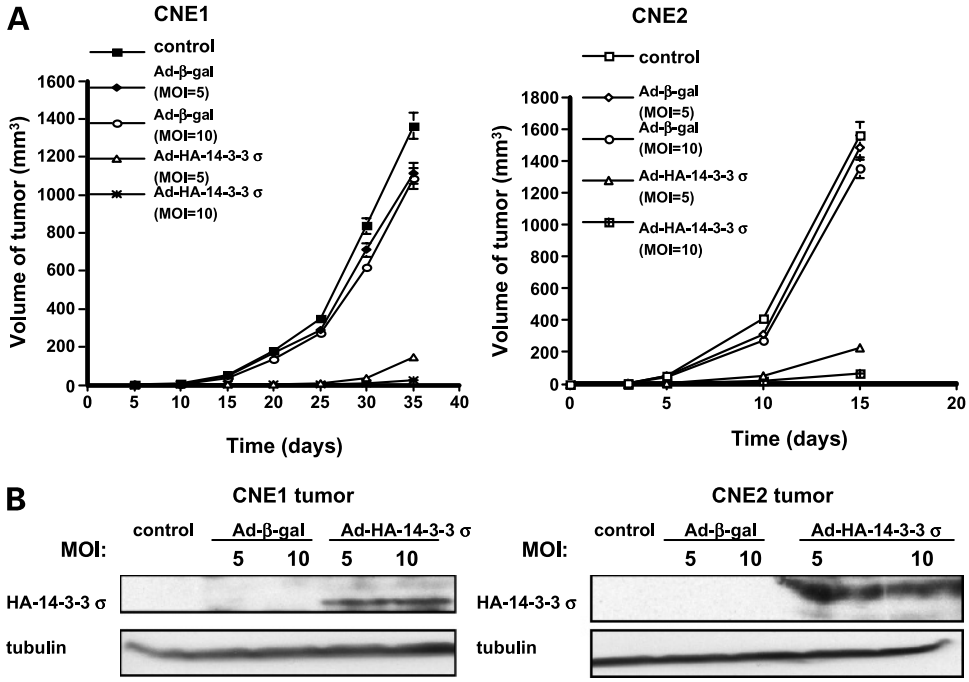

Figure 6. 14-3-3σ Inhibits tumorigenicity of NPC cells in nude mice. **A,** 14-3-3σ inhibits tumorigenicity of CNE1 and CNE2 cells. CNE1 and CNE2 cells were infected with Ad-HA-14-3-3σ or Ad-β-gal at the indicated MOIs, or were left uninfected (*control*). Cells (1×10^6) were harvested and s.c. injected into the flank region of female nude mice. Tumor volumes were monitored for the indicated number of days. *Points,* change in tumor volume; *bars,* SD. **B,** protein expression in tumor tissues. Tumor tissues from the sites of implantation as described in **A** were assessed for protein expression by immunoblotting with anti-HA (for delivered 14-3-3σ expression). Immunoblotting of tubulin indicated equal loading. Representative tumors are shown.

cells (16). The CNE1 cells were very sensitive to Adv-p16 treatment, whereas the CNE2 cells were resistant to Adv-p16 gene transfer treatment (16). In contrast, we found that 14-3-3σ inhibited both CNE1 and CNE2 cancer models equally well. This could be due to the fact that 14-3-3σ has a negative role on positive regulators of the cell cycle, such as cyclin-dependent kinase 2 (4) and Akt, and has a positive role on negative regulators of the cell cycle, such as p53 (7).

Taken together, our results indicate that 14-3-3σ inhibits the tumorigenicity of NPC cells. Our findings in demonstrating the negative role of 14-3-3σ toward Akt and in exploring 14-3-3σ as an anticancer agent have important clinical relevance. The administration of 14-3-3σ could be an excellent therapeutic regimen for the treatment of NPC.

Acknowledgments

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