Research Article

(3-Chloroacetyl)-indole, a Novel Allosteric AKT Inhibitor, Suppresses Colon Cancer Growth In Vitro and In Vivo

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Abstract

Indole-3-carbinol (I3C) is produced in Brassica vegetables such as broccoli and cabbage and has been shown to inhibit proliferation and induce apoptosis in various cancer cells, including breast, prostate, colon, and leukemia. However, only high doses of I3C were shown to inhibit cell proliferation (IC50 = 200–300 µmol/L). Our goal here was to develop a more potent antitumor agent by modifying the structure of I3C. We created I3C derivatives and found that (3-chloroacetyl)-indole (3CAI) more strongly inhibited colon cancer cell growth than I3C. In addition, by screening 85 kinases in a competitive kinase assay, we found that 3CAI was a specific AKT inhibitor. AKT is a serine/threonine kinase that plays a pivotal role in promoting transformation and chemoresistance by inducing proliferation and inhibiting apoptosis. Therefore, AKT is regarded as a critical target for cancer therapy. 3ICA, a derivative of I3C, is a potent and specific AKT inhibitor. This compound showed significant inhibition of AKT in an in vitro kinase assay and suppressed expression of AKT direct downstream targets such as mTOR and GSK3β as well as induced growth inhibition and apoptosis in colon cancer cells. In addition, oral administration of this potent AKT inhibitor suppressed cancer cell growth in an in vivo xenograft mouse model. Cancer Prev Res; 4(11); 1–10. ©2011 AACR.

Introduction

Indole-3-carbinol (I3C), a natural product found in broccoli and cabbage, has chemopreventive properties such as antiproliferative and proapoptotic activities against various cancers (1, 2). It reportedly targets a broad range of signaling pathways involved in cell-cycle regulation and survival, including those mediated by AKT, NF-xB, Bcl-2, mitogen-activated protein kinases, cyclin-dependent kinase (CDK) inhibitors, and cyclin D1 in vitro (3–5). It is also reported to protect against chemically induced carcinogenesis in vivo (6–8). These previous studies suggest that many dietary plants produce unique compounds that could be a source of starting molecules from which to synthetically develop new chemotherapeutic molecules with potent anti-cancer properties.

AKT/PKB is a serine/threonine kinase that belongs to the AGC family of kinases (9). Three members, AKT1, AKT2, and AKT3, have been identified and are composed of a conserved N-terminal pleckstrin homology (PH) domain, a central catalytic domain, and a C-terminal regulatory hydrophobic motif. The PH domain directs AKT translocation from the cytosol to the plasma membrane by binding to the membrane lipids phosphatidylinositols-3,4,5-P3, which are products of phosphoinositide 3-kinase (PI3K). The AKT kinases are activated by phosphorylation of a threonine residue (Thr308) in the activation loop and a serine residue (Ser473) in the COOH-terminal domain (10, 11). The PI3K/AKT pathway regulates many cellular functions through a wide range of downstream targets, including the tuberous sclerosis complex 2 (TSC2), which negatively regulates the mTOR. Phosphorylation of TSC2 by AKT releases mTOR activity, which can stimulate protein synthesis in response to nutrients as well as regulate cell growth (12, 13). Another major substrate of AKT is glycogen synthesis kinase 3B (GSK3B), which is inactivated by AKT phosphorylation leading to increased glycogen synthesis during glucose metabolism following insulin stimulation (14, 15). The PI3K signaling pathway is genetically altered in numerous types of cancers. For example, activating mutations of PIK3CA or mutations of PTEN are found in tumors of the colon, breast, brain, prostate, stomach, and many other organs (16). AKTs are good candidates for mediating PI3K-dependent cell survival responses. Indeed, AKT activation and overexpression are often

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associated with resistance to chemotherapy or radiotherapy, and dominant-negative mutants of AKT enhance the cytotoxicity of chemotherapeutic agents (17–19). In contrast, only a few AKT inhibitors have been identified (20). Thus, development of AKT inhibitors should be useful in clinical cancer therapy. Herein, we report that the I3C, (3-chloroacetyl)-indole (3CAI) is a potent allosteric and clinical cancer therapy. Herein, we report that the I3C, (3-chloroacetyl)-indole (3CAI) is a potent allosteric and specific AKT inhibitor that exerts efficacy in vitro and in vivo.

Materials and Methods

Reagents

I3C (purity: 95%) was purchased from Sigma-Aldrich. 3CAI (purity: 95%), 5-methoxy-3CAI (purity: 95%), 5-fluoro-3CAI (purity: 95%), and 2-(4-(2-hydroxyethyl) piperazin-1-yl)-1-(5-methoxy-1H-indol-3-yl)ethanone (purity: 95%) were purchased from InterBioScreen. CNBr-Sepharose 4B beads were purchased from GE Healthcare. Active AKTs, active MAP1/ERK1 kinase (MEK1), active c-Jun-NH2-kinase 1 (JNK1), active extracellular signal–regulated kinase 1 (ERK1) human recombinant protein, and histone H2B and H2AX for kinase assays, were purchased from Millipore. The active TOPK human recombinant protein for the kinase assay was purchased from SignalChem. PI3K was obtained from Upstate Biotechnology. AKT, phospho-AKT (p-AKT; Thr308), mTOR, phospho-mTOR (p-mTOR; Ser2448), GSK3β, phospho-GSK3β (p-GSK3β; Ser9), Bad, Bcl-2, and phospho-ASK1 (p-ASK1; Ser83) and CDKN1A antibodies were purchased from Cell Signaling Technology. Antibodies to detect p53 and β-actin were purchased from Santa Cruz Biotechnology. LY294002 was purchased from Gibco BRL. AKT inhibitor VIII was purchased from Merck KGaA.

Synthesis of 3CAI

3CAI (purity: 95%) was synthesized as described (21), and purity and structure were analyzed by high-performance liquid chromatography and nuclear magnetic resonance.

Cell culture

All cell lines were purchased from American Type Culture Collection and were cytogenetically tested and authenticated before the cells were frozen. Each vial of frozen cells was thawed and maintained in culture for a maximum of 8 weeks. Enough frozen vials were available for each cell line to ensure that all cell-based experiments were conducted on cells that had been tested and in culture for 8 weeks or less. HCT116 and HT29 human colon cancer cells were cultured in McCoy’s 5A medium (McCoy’s 5A supplemented with 10% FBS and 1% antibiotics) were added to 0.6% agar, with different doses of each compound in a base layer and a top layer of 0.3% agar. The cultures were maintained at 37°C in a 5% CO2 incubator for 3 weeks and then colonies were counted under a microscope using the Image-Pro Plus software (v.4) program (Media Cybernetics).

Western blot analysis

Cell lysates were prepared with radioimmunoprecipitation assay buffer (50 mmol/L Tris-HCl, pH 7.4, 1% NP-40, 0.25% sodium deoxycholate, 0.1% SDS, 150 mmol/L NaCl, 1 mmol/L EDTA, and 1× protease inhibitor tablet). Equal amounts of protein were determined by the bicinchoninic acid assay (Pierce). Proteins were separated by SDS-PAGE and transferred to polyvinylidene difluoride membranes (Amersham Pharmacia Biotech). Membranes were blocked with 5% nonfat dry milk for 1 hour at room temperature and incubated with appropriate primary antibodies overnight at 4°C. After washing with PBS containing 0.1% Tween 20, the membrane was incubated with a horseradish peroxidase (HRP)–conjugated secondary antibody at 1:5,000 dilution, and the signal was detected with a chemiluminescence reagent (Amersham Biosciences Corp).

In vitro pull-down assay

Recombinant human AKTs (200 ng) were incubated with 3CAI-Sepharose 4B (or Sepharose 4B only as a control) beads (50 μL; 50% slurry) in reaction buffer [50 mmol/L Tris, pH 7.5, 5 mmol/L EDTA, 150 mmol/L NaCl, 1 mmol/L dithiothreitol (DTT), 0.01% NP-40, and 2 μg/mL bovine serum albumin]. After incubation with gentle rocking overnight at 4°C, the beads were washed 5 times with buffer (50 mmol/L Tris, pH 7.5, 5 mmol/L EDTA, 150 mmol/L NaCl, 1 mmol/L DTT, and 0.01% NP-40) and binding was visualized by Western blotting.

Cell proliferation assay

Cells were seeded (1 × 10^3 cells per well) in 96-well plates, incubated for 24 hours, and then treated with...
different doses of each compound. After incubation for 48 hours, 20 μL of CellTiter 96 AQ aqueous One Solution (Promega) was added and then cells were incubated for 1 hour at 37°C in a 5% CO₂ incubator. Absorbance was measured at 492 nm.

**Apoptosis assay**
Colon cancer cells were plated into 60-mm culture dishes (1 x 10⁵ cells per dish) and incubated for 1 day in medium containing 10% FBS. The culture medium was then replaced with a 1% serum medium and cultured for 4 days with 3CAI, I3C, or a commercial AKT inhibitor. The cells were collected by trypsinization and washed with PBS. The cells were resuspended in 200 μL of binding buffer. Annexin V staining was accomplished following the product instructions (Clontech). The cells were observed under a fluorescence microscope equipped a dual filter set for fluorescein isothiocyanate and propidium iodide and then analyzed by flow cytometry.

**In vitro kinase assay**
The kinase assay was conducted in accordance with instructions provided by Upstate Biotechnology. Briefly, the reaction was carried out in the presence of 10 μCi of [γ-³²P]ATP with each compound in 40 μL of reaction buffer containing 20 mmol/L HEPES (pH 7.4), 10 mmol/L MgCl₂, 10 mmol/L MnCl₂, and 1 mmol/L DTT. After incubation at room temperature for 30 minutes, the reaction was stopped by adding 10 μL protein loading buffer, and the mixture was separated by SDS-PAGE. The relative amounts of incorporated radioactivity were assessed by autoradiography.

**Hematoxylin–eosin staining and immunohistochemistry**
Tumor tissues from mice were embedded in a paraffin block and subjected to hematoxylin and eosin (H&E) staining and immunohistochemistry. Tumor tissues were deparaffinized and hydrated, then permeabilized with 0.5% Triton X-100/1% PBS for 10 minutes, hybridized with Ki-67 (1:500) as the primary antibody, and HRP-conjugated goat anti-rabbit or mouse IgG antibody was used as secondary antibody. After developing with 3,3′-diaminobenzidine, the sections were counterstained with H&E. All sections were observed by microscope and the Image-Pro Plus software (v.4) program (Media Cybernetics).

**Xenograft mouse model**
Athymic mice [Cr:NIH(S), NIH Swiss nude, 6- to 9-week old] were obtained from Charles River and were maintained under “specific pathogen-free” conditions.
Figure 2. Effect of 3CAI on AKT activity. A, 3CAI suppresses AKT1 kinase activity in vitro. The effect of 3CAI on AKT1, MEK1, JNK1, ERK1, or TOPK activity was assessed by an in vitro kinase assay using AKT1 (active; 100 ng), histone H2B (AKT substrate; 500 ng), MEK1 (active; 400 ng), inactive ERK2 (MEK1 substrate; 500 ng), JNK1 (active; 50 ng), c-jun (JNK1 substrate; 500 ng), ERK1 (active; 400 ng), inactive RSK2 (ERK1 substrate; 500 ng), TOPK (active; 500 ng), or histone H2AX (TOPK substrate; 500 ng) with [γ-32P]ATP. B, 3CAI inhibits PI3K kinase activity at the highest concentration in vitro. The inhibitory effect of 3CAI or LY294002 as a PI3K inhibitor on PI3K activity was assessed by an in vitro kinase assay. The conversion of phosphatidylinositol-4-phosphate to phosphatidylinositol trisphosphate was determined by autoradiography. 3CAI substantially inhibits AKT1 (C) or AKT2 (D) kinase activity in a dose-dependent manner. The inhibitory effect of 3CAI, I3C, or an AKT inhibitor VIII on AKT1 or AKT2 activity was assessed by an in vitro kinase assay. The 32P-labeled substrate was visualized by autoradiography. Band density was measured by the Image J program. All data are represented as means ± SD of values from 3 independent experiments. *, significant (P < 0.05) decrease caused by 3CAI, LY294002, or AKT inhibitor VIII compared with untreated control.

Statistical analysis

All quantitative results are expressed as mean values ± SD. Statistically significant differences were obtained by Student's t test or by one-way ANOVA. A value of P < 0.05 was considered to be statistically significant.

Results

An I3C derivative, 3CAI, suppresses colon cancer cell growth

We screened for I3C derivatives that could effectively inhibit proliferation and anchorage-independent cell growth. To compare the effects of I3C (Fig. 1A) and its derivatives (Fig. 1B) on cancer cell growth, HCT116 colon cancer cells were treated with various concentrations of I3C or its derivatives for 48 hours. Proliferation was assessed by MTS assay and results indicated that growth was significantly decreased by I3C derivatives (#1, #2

based on the guidelines established by the University of Minnesota Institutional Animal Care and Use Committee. Mice were divided into 5 groups as follows: (i) untreated vehicle group (n = 15), (ii) 20 mg 3CAI/kg of body weight (n = 15), (iii) 30 mg 3CAI/kg of body weight (n = 15), (iv) 100 mg I3C/kg of body weight (n = 15), and (v) no cells and 30 mg 3CAI/kg of body weight (n = 15). HCT116 cells (3 × 10⁶ cells/100 μL) were suspended in serum-free McCoy's 5A medium and inoculated subcutaneously into the right flank of each mouse. 3CAI, I3C, or vehicle was administered orally 5 times per week for 21 days. Tumor volume was calculated from measurements of 2 diameters of the individual tumor base according to the following formula: tumor volume (mm³) = (length × width × height × 0.52). Mice were monitored until tumors reached 1-cm³ total volume, at which time mice were euthanized and tumors were extracted.
or #3) but I3C or derivative 4 had little effect (Fig. 1C). In addition, we compared the effect of the 5 compounds on anchorage-independent cell growth. HCT116 colon cancer cells were seeded with I3C or its derivatives in 0.3% agar and incubated for 3 weeks. Data showed that only the high dose of I3C (200 μmol/L) or I3C derivatives (#1, #2, or #3), but not derivative 4, strongly suppressed anchorage-independent cell growth (Fig. 1D). Interestingly, I3C derivatives 2 or 3 had inhibitory effects on growth similar to derivative 1. Therefore, these findings suggested that methoxy and fluoro modification of 3CAI was not important for inhibiting proliferation or anchorage-independent cell growth. On the basis of these results, 3CAI seems to be the most effective anti–colon cancer compound of the 4 derivatives tested and was used in further studies.

3CAI is a potent inhibitor of AKT kinase activity
To identify the direct molecular target of 3CAI, we screened 85 kinases against 3CAI in a high-throughput...
of potent AKT1 inhibitor than PI3K (60% inhibition at 1 μmol/L). These data showed that 3CAI is a potent AKT1 activity (Fig. 2C) and AKT2 activity (Fig. 2D) in a dose-dependent manner. These data showed that 3CAI is a potent and specific AKT1 and AKT2 inhibitor.

3CAI directly binds with AKT1 or AKT2 in an ATP noncompetitive manner
We next conducted a molecular docking study with 3CAI and AKT1 and AKT2 to determine its binding orientation. The docking score of 3CAI with AKT1 was −2.03 kcal/mol, which was a little less favorable than the docking score of 3CAI with AKT2 (−2.25 kcal/mol). 3CAI forms a hydrogen bond with Glu17 in the AKT1 PH domain, whereas 3CAI forms 3 hydrogen bonds with Lys14, Leu52, and Arg86 in the AKT2 PH domain (Fig. 3A). The structures of AKT1 or AKT2 were aligned and superimposed to compare the docked conformation of 3CAI. 3CAI adopts a configuration parallel to Ins(1,3,4,5)P4 in AKT1, whereas 3CAI adopts a configuration perpendicular to Ins(1,3,4,5)P4 in AKT2 (Fig. 3B). To confirm the results of the computer docking model, we conducted in vitro pull-down assays using 3CAI or I3C-conjugated Sepharose 4B beads. These results showed that 3CAI directly bound to recombinant AKT1 (Fig. 4A) and AKT2 (Fig. 4B) in an ATP noncompetitive manner. 3CAI showed no binding. Similar results were obtained with an HCT116 colon cancer cell lysate (Fig. 4C and D). These results suggest that 3CAI binds to an AKT allosteric site and not the ATP pocket.

3CAI inhibits downstream targets of AKT and induces apoptosis
We investigated the effect of 3CAI on downstream targets of AKT, including the phosphorylation of mTOR.
and GSK3β. Results indicated that the AKT-mediated phosphorylation site of mTOR(Ser2448) and GSK3β (Ser9) was substantially decreased by 3CAI in a time-dependent manner (Fig. 5A). However, phosphorylation of AKT(Thr308) was not changed. Furthermore, the proapoptotic marker proteins p53 and p21 were also upregulated by 3CAI after 12 or 24 hours of treatment. In addition, the antiapoptotic marker protein Bcl-2 and proapoptotic marker proteins p53 and p21 were also upregulated by 3CAI after 12 or 24 hours of treatment. These findings suggested AKT-mediated phosphorylation of ASK1(Ser83) were significantly decreased (Fig. 4B). These findings suggested that pro- or antiapoptotic marker proteins are regulated by 3CAI in colon cancer cells. Next, to determine whether apoptosis was induced by 3CAI, we compared the effect on cell death of this compound, I3C, and an AKT inhibitor. HCT116 and HT29 colon cancer cells were seeded on 6-cm dishes in 1% FBS/McCoy’s 5A (HCT116) with 3CAI, I3C, or the AKT inhibitor and then incubated for 4 days. Results showed that the number of apoptotic cells was significantly increased by 3CAI in HCT116 and HT29 colon cancer cells compared with untreated control cells (Fig. 5C).

3CAI inhibits growth of colon cancer cells in a xenograft model

To examine the antitumor activity of 3CAI in vivo, HCT116 cancer cells were injected into the right flank of individual athymic nude mice. Mice were orally administered 3CAI at 20 or 30 mg/kg, I3C at 100 mg/kg, or vehicle 5 times a week for 21 days. Treatment of mice with 30 mg/kg of 3CAI significantly suppressed HCT116 tumor growth by 50% relative to the vehicle-treated group (Fig. 6A; \( P < 0.05 \)). Remarkably, mice seemed to tolerate treatment with these doses of 3CAI without overt signs of toxicity or significant loss of body weight compared with vehicle-treated group (Fig. 6B). The effects of 3CAI on a tumor proliferation marker were evaluated by immunohistochemistry and H&E staining of HCT116 tumor tissues after the 21 days of treatments. The expression of Ki-67 was markedly decreased by treatment with 3CAI (Fig. 6C). Next, we examined the effect of 3CAI on downstream targets of AKT such as phosphorylation of mTOR and GSK3β by Western blot, using the in vivo tumor tissues. Expression of these AKT-target proteins was strongly suppressed by 30 mg/kg of 3CAI.
in tumor tissues (Fig. 6D). These data suggested that HCT116 colon tumor development was suppressed by 3CAI through inhibition of AKT signaling pathway.

Discussion

The natural phytochemical I3C has been reported to exert potent antiproliferative activities in cell-based studies and has been implicated as a potential therapy for human cancers. However, only high concentrations of I3C can induce anticancer activity and seem to involve a nonspecific broad range of targets. Therefore, interest in developing more potent synthetic I3C-based compounds has grown. However, only a few I3C analogues have been reported and exert only a low enhancement of potency in biological activity (23, 24). In contrast, 1-benzyl-I3C was reported as the most potent synthetic derivative of I3C with an approximate 1,000-fold increased potency against breast cancer. The investigators suggested that 1-benzyl-I3C inhibited CDK2 enzymatic activity and CDK6 activity through the downregulation of CDK6 transcription and protein expression (25). However, direct targets of 1-benzyl-I3C or its specificity were not determined. We have identified a potent derivative of I3C, 3CAI, from a high-throughput screening...
of 85 kinases (Supplementary Table S1). We found that 3CAI inhibited only AKT kinase activity (Fig 2A and B), suggesting that 3CAI is a specific AKT inhibitor.

In addition, we determined the binding orientation between 3CAI and AKT by a computer docking model. About 20 crystal structures of AKT2 and 10 of AKT1 are available. The molecular alignment of the protein sequences using EMBOSS (26) showed that they possess about 85% and 92% identity. 3CAI was docked to the allosteric site of AKT1 and AKT2. The preference for AKT2 over AKT1 is much more difficult to explain because the crystal structure of the AKT2 PH domain has not yet been solved. The sequences of AKT1 and AKT2 are highly conserved, and the sequence identity between the PH domains is about 80%. Thus, a reliable homology model of the AKT2 PH domain can be built on the basis of the known structure of the AKT1 PH domain. The structure of the AKT2 PH domain used in this study was modeled on the template structure of 1UNQ. The reason as to why 3CAI prefers the allosteric site of AKT1 and AKT2 to the ATP site is puzzling. The observed preference might not lie in a classical explanation where specific ligand–protein noncovalent interactions do or do not exist, but potentially the explanation lies in the realm of statistics. 3CAI was computationally predicted to possess multiple binding orientations within the ATP-binding site of both AKT1 and AKT2 (data not shown). However, 3CAI preferred to dock only to the PH domain in AKT1 and AKT2 (Fig. 3A and B). Therefore, we needed to analyze a docking simulation between 3CAI and the AKT1 and AKT2 proteins as well as examine binding with a deletion mutant of AKT1 and AKT2.

Previous studies showed that HER-2 mediated AKT activation to induce translocation of MDM2 from the cytoplasm to the nucleus. MDM2 directly binds to p53 and induces ubiquitination (27, 28). In other reports, an effect of AKT on MDM2 subcellular localization from the cytoplasm to the nucleus was not detected, but AKT was shown to facilitate the function of MDM2 to promote p53 ubiquitination by phosphorylation of Ser186 (29). In our study, the protein level of p53 was substantially increased by 3CAI in a time-dependent manner, as was the abundance of p21, a target of p53 (Fig. 5B). We examined whether inhibition of AKT kinase activity by 3CAI could induce stability of p53 by suppressing phosphorylation of MDM2 (Ser166). We confirmed the phosphorylation of MDM2 and p53 protein level by an immunofluorescence assay and Western blot analysis of cytoplasmic and nuclear protein fractions. However, we did not observe any significant translocation of MDM2 (data not shown). Importantly, 3CAI suppressed colon cancer cell growth and induced apoptosis more potently than I3C or a commercially available AKT inhibitor (Fig. 5). Results of a xenograft mouse model showed that oral administration of 3CAI at 30 mg/kg of body weight for 21 days significantly inhibited colon cancer cell growth and was not toxic (Fig. 6A and B).

In conclusion, we found that the I3C derivative 3CAI is a potent and specific AKT inhibitor and suppressed cell growth and induced apoptosis both in vitro and in vivo. These findings should be useful for developing drugs targeting AKT, and 3CAI seems to be a promising lead compound.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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