Identification of a Small Molecule with Synthetic Lethality for K-Ras and Protein Kinase C Iota

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Abstract

K-Ras mutations are frequently found in various cancers and are associated with resistance to treatment or poor prognosis. Similarly, poor outcomes have recently been observed in cancer patients with overexpression of protein kinase C iota (PKCζ), an atypical protein kinase C that is activated by oncogenic Ras protein and is required for K-Ras–induced transformation and colonic carcinogenesis in vivo. Thus far, there is no effective agent for treatment of cancers with K-Ras mutations or PKCζ overexpression. By synthetic lethality screening, we identified a small compound (designated oncrasin-1) that effectively kills various human lung cancer cells with K-Ras mutations at low or submicromolar concentrations. The cytotoxic effects correlated with apoptosis induction, as was evidenced by increase of apoptotic cells and activation of caspase-3 and caspase-8 upon the treatment of oncrasin-1 in sensitive cells. Treatment with oncrasin-1 also led to abnormal aggregation of PKCζ in the nucleus of sensitive cells but not in resistant cells. Furthermore, oncrasin-1–induced apoptosis was blocked by siRNA of K-Ras or PKCζ, suggesting that oncrasin-1 is targeted to a novel K-Ras/PKCζ pathway. The in vivo administration of oncrasin-1 suppressed the growth of K-ras mutant human lung tumor xenografts by >70% and prolonged the survival of nude mice bearing these tumors, without causing detectable toxicity. Our results indicate that oncrasin-1 or its active analogues could be a novel class of anticancer agents, which effectively kill K-Ras mutant cancer cells. [Cancer Res 2008;68(18):7403–8]

Introduction

Activating mutations of three oncogenic Ras genes—H-Ras, K-Ras, and N-Ras—play important roles in tumorigenesis and the maintenance of malignant phenotypes (1). Among them, K-Ras mutations are the most frequently found in tumors, especially adenocarcinomas of the pancreas, colon, and lung (1, 2). K-Ras mutations are also associated with resistance to chemotherapy and radiotherapy and, thus, a poor prognosis (3). Therefore, mutant Ras proteins are important targets for anticancer therapy.

As a subfamily of small guanine nucleotide-binding proteins, Ras proteins cycle between an active GTP-bound form and an inactive GDP-bound form (4). Binding of Ras with GTP is facilitated by guanine nucleotide exchange factors through catalyzing the release of GDP and is required for the interaction of Ras with target proteins (5). Ras mutations that diminish the GTPase activity or decrease the GDP binding capacity render Ras constitutively active and GTP bound. Ras protein can also be activated by other mechanisms. In the absence of a Ras mutation, increased Ras activity is frequently detected in human cancer because of gene amplification (6), overexpression, and an increase in upstream signals from tyrosine-kinase growth factor receptors such as Her2 (7).

Because Ras proteins must be translocated to the inner leaflet of the plasma membrane to be activated, agents were developed that interrupt the posttranslational modifications required for Ras trafficking to the plasma membrane as a means of suppressing Ras function. One group of such agents is the farnesyltransferase inhibitors (FTI), which have now been intensively investigated in preclinical and clinical trials as a cancer therapy (8). This approach, however, may be effective in preventing the membrane translocation of H-Ras, but not K-Ras and N-Ras, because in the presence of FTIs, N-Ras and K-Ras proteins are geranylgeranylated and transferred to the membrane (9, 10). Several phase II and phase III clinical trials also showed that FTIs did not have significant single-agent activity in lung, pancreatic, colorectal, bladder, and prostate cancers (8). Thus, compounds with novel mechanisms of action and high specificity for cancer cells with hyperactive Ras will be valuable for anticancer therapy.

Synthetic lethality screening has recently emerged as a new approach to identify cytotoxic agents targeted to cancer cells with mutations in a particular gene (11). Using genetically defined cell lines to screen compounds that kill cells with a particular mutant gene only but not the normal counterparts will allow us to identify compounds that target to a protein whose functional change is synthetic lethal to an inactivated tumor suppressor gene or an activated oncogene. Using this approach, we identified a small molecule that can effectively kill K-Ras mutant cancer cells but not normal isogenic cells or H-Ras or N-Ras mutant cancer cells. The mechanistic studies revealed that apoptosis induction by this compound is blocked by knockdown of K-Ras or protein kinase C iota (PKCζ), suggesting that oncrasin-1 is synthetic lethal to active K-Ras and PKCζ.

Materials and Methods

Cell lines. The human non–small cell lung carcinoma H1299, H322, H460, H358, H2887, H2087, and A549 cell lines were routinely propagated in a monolayer culture in RPMI 1640 supplemented with 10% heat-inactivated FCS, 100 units/mL penicillin, and 100 mg/mL streptomycin. The establishing of T29, T29Kt1, and T29Ht1 cells and in vitro and in vivo biological characterization of those cell lines have been reported previously (12). In vitro cell growth and/or cell cycle progression of those three cell lines were similar. The cells were maintained in DMEM with the same supplements. All cells were maintained in the presence of 5% CO2 at 37°C.

Chemicals and antibodies. A chemical library with 10,000 compounds, including oncrasin-1, was obtained from Chembridge Corporation. The chemicals in the library are provided at a concentration of 5 mg/mL in 0.1% DMSO.
DMSO. Antibodies to the following proteins were used for the Western blot analysis: PKCα, PKCβ, Raf-1, and caspase-3 (Santa Cruz Biotechnology); caspase-8 (PharMingen); and β-actin (Sigma).

**Cell viability assay.** The inhibitory effects of oncrasin-1 and other agents on cell growth were determined by using the sulforhodamine B (SRB) assay, as described previously (13). Each experiment was performed in quadruplicate and repeated at least thrice. The IC50 value, a dose that causes a 50% reduction in surviving cells compared with the number of control cells, was determined by using the CurveExpert Version 1.3 program.

**Flow cytometry assay.** Cells were seeded at a density of $1 \times 10^5$ cells per dish in 100-mm dishes and allowed to grow overnight. After the treatment, cells were harvested with trypsin and washed twice with PBS. Cells were fixed with 75% ethanol at the cell density of $1 \times 10^5$ cells/mL overnight. Next, the cell pellets were harvested and resuspended with propidium iodide (PharMingen) for 15 min in the dark at room temperature. The cells were analyzed using an EPICS Profile II flow cytometer (Coulter Corp.) with the Multicycle Phoenix Flow Systems program (Phoenix Flow Systems). All experiments were repeated thrice.

**Western blot and immunofluorescent staining.** Western blot analysis was performed as we have previously described (14). For immunofluorescent staining, cells were seeded at a density of $1 \times 10^5$ cells per well in 6-well plates containing a 1% gelatin–treated cover slide. Cells were allowed to grow overnight. Cells were treated with different compounds or radiation as indicated. After the treatment, cells were washed with PBS twice, then fixed with 2% paraformaldehyde at the cell density of $1 \times 10^5$ cells/mL overnight. Next, the cell pellets were harvested and resuspended with propidium iodide (PharMingen) for 15 min in the dark at room temperature. The cells were analyzed using an EPICS Profile II flow cytometer (Coulter Corp.) with the Multicycle Phoenix Flow Systems program (Phoenix Flow Systems). All experiments were repeated thrice.

**Animal experiments.** Animal experiments were carried out in accordance with Guidelines for the Care and Use of Laboratory Animals (NIH publication number 85–23) and the institutional guidelines of M. D. Anderson Cancer Center. S.c. tumors were established in 4- to 6-wk-old female nude mice (Charles River Laboratories, Inc.) by inoculation of $1.5 \times 10^6$ H460 cells into the dorsal flank of each mouse. After the tumors grew to 2 to 3 mm in diameter, the mice were treated with i.p. administration of oncrasin-1 at a dose of 100 mg/kg/d (dissolved in 0.5 mL solvent containing 10% DMSO, 10% Cremophore EL, and 10% ethanol) or solvent alone. Tumor volumes were calculated by using the formula $A \times B \times C/2$, where $A$ and $B$ represent the larger and smaller diameters, respectively. Mice were killed when the tumors grew to 15 mm in diameter. To evaluate the toxicity of treatment, blood samples were collected from the tail vein before treatment, and 2 d after the last treatment, and serum alanine transaminase, aspartate transaminase, blood urea nitrogen, and creatinine levels were determined as described elsewhere (15).

**Statistical analysis.** Differences between the treatment groups were assessed by ANOVA using statistical software (StatSoft). Differences between the results of the in vivo tumor growth experiment were assessed using ANOVA with a repeated measurement module. $P$ values of <0.05 were regarded as significant.

**Results**

**Library screening for oncogenic Ras-targeted compounds.** We used human ovarian surface epithelial cells immortalized with the catalytic subunit of human telomerase reverse transcriptase and the SV40 early genomic region (designated T29), and its tumorigenic derivatives transformed with either mutant H-Ras (T29Ht1) or mutant K-Ras (T29Kt1; ref. 12), to screen a chemical library from Chembridge Corporation for compounds that showed an ability to selectively kill tumor cells. Cells seeded in a 96-well plate were treated with each compound at a final concentration of $\sim 5$ μg/mL (20–30 μmol/L). Cells treated with solvent (DMSO) were used as controls. A lethal effect was determined in a SRB

**Table 1. Library screening for oncogenic Ras-targeted compounds.**

<table>
<thead>
<tr>
<th>Cell lines</th>
<th>Ras gene</th>
<th>p53</th>
<th>IC50 (μmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H460</td>
<td>K-Ras 61H</td>
<td>Wt</td>
<td>0.25</td>
</tr>
<tr>
<td>H2122</td>
<td>K-Ras 12C</td>
<td>176F</td>
<td>1.0</td>
</tr>
<tr>
<td>A549</td>
<td>K-Ras 12S</td>
<td>Wt</td>
<td>1.58</td>
</tr>
<tr>
<td>A2887</td>
<td>K-Ras 12C</td>
<td>UD</td>
<td>0.11</td>
</tr>
<tr>
<td>H2087</td>
<td>N-Ras 61K</td>
<td>157F</td>
<td>&gt;31</td>
</tr>
<tr>
<td>H1299</td>
<td>N-Ras</td>
<td>Deleted</td>
<td>&gt;31</td>
</tr>
<tr>
<td>H322</td>
<td>Wt</td>
<td>248L</td>
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<td>Wt</td>
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<td>31</td>
</tr>
<tr>
<td>HBEC</td>
<td>UD</td>
<td>UD</td>
<td>&gt;31</td>
</tr>
</tbody>
</table>

Figure 1. Library screening. A, chemical structure of oncrasin-1. B, dose effect of oncrasin-1 in T29, T29Ht1, and T29Kt1 cells. The cells were treated with various concentrations (ranging from 0.1–33 μmol/L) of oncrasin-1. Cell viability was determined 3 d after treatment by SRB assays. Control cells were treated with solvent (DMSO), and their value was set as 1. C, dose-response in human lung cancer cell lines. Lung cancer cells with various oncogenic Ras gene status were treated with oncrasin-1 at various concentrations. Cell viability was determined as in B. Points, mean of two assays done in quadruplicate; bars, SD. Control cells were treated with solvent (DMSO), and their value was set as 1. D, the status of Ras gene and p53 gene mutations, and IC50 of oncrasin-1 in lung cancer cell lines tested in C. Based on published data and the Cancer Genome Project Database, Wt, wild-type; UD, unknown; HBEC, human bronchial epithelial cells.
The doses of oncrasin-1 did not induce detectable cleavages of the caspases, indicating that it effectively killed K-Ras-mutant H460, H2122, and H2887, and A549 cells with an IC₅₀ of ≤3 μmol/L (Fig. 1C). However, oncrasin-1 had minimal effects on normal human bronchial epithelial cells. It also had minimal effects on H322 and H1395 lung cancer cells, which have wild-type Ras genes, and on H1299 and H2087 lung cancer cells, which harbor mutant N-Ras genes. Those results suggested that oncrasin-1 is effective against various lung cancer cells with K-Ras mutations.

**Induction of apoptosis by oncrasin-1.** Chemically, this compound has the same core structure as indole-3-carbinol, a naturally occurring constituent of many plant food that has been tested for the prevention and treatment of cancer (16). It has also structural similarity to lonidamine (17), which have been evaluated preclinically and clinically for treatment of cancers. However, both indole-3-carbinol and lonidamine did not have any cytotoxic effects in T29, T29Kt1, T29Ht1, and H460 cells at any of the concentrations tested (up to 100 μmol/L; data not shown), suggesting that oncrasin-1 may have different anticancer mechanisms from those two agents.

To determine whether the antitumor activity of oncrasin-1 is due to the suppression of cell proliferation or to cell killing, we performed flow cytometric analysis after treatment with oncrasin-1 at 10 μmol/L (for T29 or T29Kt1 cells) or 1 μmol/L (for H460 cells), the doses of ~IC₅₀ for T29Kt1 and H460, respectively. At 12 hours after the treatment with oncrasin-1, apoptotic cells account for 47.2% in H460 and 33.2% in T29Kt1 cells (Fig. 2A). In contrast, apoptotic cells in H460 and T29Kt1 cells, which were treated with DMSO, and in the T29 cells treated with control siRNA were <3%. This result indicated that oncrasin-1 can effectively induce cell killing in T29Kt1 and H460 cells and that apoptosis induction is a major mechanism of oncrasin-1–induced cell killing. Western blot analysis showed further that the treatment of H460 cells with 1 μmol/L oncrasin-1 effectively activated caspases 3 and 8 (Fig. 2B), whereas treatment with DMSO or indole-3-carbinol at 30 μmol/L did not induce detectable cleavages of the caspases, indicating that its cytotoxic effect in cancer cells is due to its induction of apoptosis.

**K-Ras is required for effective apoptosis induction by oncrasin-1.** Because oncrasin-1 was identified by synthetic lethality screening of K-Ras-mutant cells, we investigated the role of the K-Ras gene in oncrasin-induced cell death. We treated H460 cells with 200 pmol/L K-Ras–specific siRNA or control siRNA for 24 hours. The cells were then treated with DMSO or 1 μmol/L oncrasin-1. After another 12 hours, the cells were harvested for apoptosis detection using fluorescence-activated cell sorting analysis. The cell lystate was also used to detect K-Ras gene expression. The results showed that treatment with K-Ras–specific siRNA but not with control siRNA suppressed K-Ras expression in H460 cells. Cells transfected with either K-Ras siRNA or control siRNA alone had a background apoptosis level of ~9% to 11%. Nevertheless, in cells treated with control siRNA, oncrasin-1 resulted in an increase of ~17% of apoptotic cells, compared with that of DMSO + siRNA–treated cells. In contrast, in K-Ras siRNA–treated cells, treatment with oncrasin-1 yielded only ~3% increase in apoptotic cells when compared with DMSO + siRNA–treated cells (Fig. 3). This result showed that K-Ras activity is required for oncrasin-1 to induce apoptosis in H460 cells.

**Oncrasin-1 induced abnormal aggregation of PKCζ in nucleus.** To investigate the molecular mechanisms of apoptosis induction by oncrasin-1, we determined the levels and/or phosphorylation status of several proteins that are involved in apoptosis and/or Ras signaling pathways, including Bax, Btk, Bcl2, and Bcl-XL in apoptosis pathway, and Raf-1, B-Raf, Akt, and the atypical PKC (aPKC), PKCζ, and PKCα in Ras signaling pathway. Western blot analysis of those molecules produced little elucidative information about mechanisms of oncrasin-1–induced apoptosis (data not shown).

Because Ras proteins execute their biological functions mainly in cell membranes, through interacting with a diversity of membrane receptors and modulating signal transduction of a variety signaling pathways that govern cell growth, proliferation, differentiation, and death, we then tested the subcellular localization of several molecules involved in the Ras signaling pathway. Treatment with oncrasin-1 induced no obvious changes in the subcellular localization of Ras, Akt, PKCζ, PKCα, and p53. However, a substantial change in the subcellular localization of PKCζ was detected after oncrasin-1 treatment (Fig. 4). In both H460 and T29Kt1 cells, both PKCα and PKCζ were diffusely distributed, with high concentrations or tiny dots on some area, especially in the nucleus and on the cell membrane, findings that are consistent with previous ones that aPKCs contain both nuclear localization.

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**Figure 2.** Apoptosis induction by oncrasin-1. A, T29, T29Kt1, and H460 cells were treated with 10 μmol/L (for T29 or T29Kt1) or 1 μmol/L (for H460) of oncrasin-1 and then harvested 12 h later. Apoptosis was detected by flow cytometric analysis. The number in each panel indicates percentage of apoptotic cells. B, Western blot analysis. H460 cells were treated with various concentrations of oncrasin-1 as indicated or with 30 μmol/L indole-3-carbinol (I3C), an inactive analogue, for 24 h. Activation of caspases 3 and 8 was detected by Western blot analysis. β-actin was used as the loading control.
signals and nuclear export signals and can shuttle between the cytoplasm and the nucleus (18). Whereas treatment with oncrasin-1 resulted in no obvious changes in the subcellular localization of PKC\(_{\alpha}\), the same treatment resulted in formation of large foci of PKC\(_{L}\) in nuclei of both T29Kt1 and H460 cells (Fig. 4) but not in oncrasin-1–resistant T29 and H1299 cells. We then tested whether aggregation of PKC\(_{L}\) into large nuclear foci is inducible by other chemotherapeutic agents, such as 5-fluorouracil and paclitaxel. The results showed that treatment of T29Kt1 cells with the chemotherapeutic agents 5-fluorouracil, paclitaxel, or with radiation at doses that result in cell killing similar to that caused by oncrasin-1 did not induce aggregation of PKC\(_{L}\) in the nuclei, suggesting that such aggregation is not a general phenomenon occurring in dying cells (data not shown).

**Roles of PKC\(_{L}\) in oncrasin-induced apoptosis.** To investigate the possible role of PKC\(_{L}\) in oncrasin-1–mediated cytotoxicity, we knocked down PKC\(_{L}\) in T29Kt1 cells by using plasmids encoding shRNA for PKC\(_{L}\) or PKC\(_{\alpha}\) provided by the Origene Corporation. The plasmids were transfected to T29Kt1 cells by using FuGENE 6 (Roche Diagnostics Corp.) as instructed by the manufacturer. Cells were pooled together after a brief selection with puromycin and tested for levels of PKC\(_{L}\) expression. Cell viability analysis showed that stable knockdown of PKC\(_{L}\) resulted in almost complete resistance to oncrasin-1 (Fig. 5A). The IC\(_{50}\) in PKC\(_{L}\)-knockdown T29Kt1 cells was 100 times higher than it was in parental T29Kt1 cells. This value was comparable with that of oncrasin-resistant T29 cells. In contrast, transfection with PKC\(_{\alpha}\) shRNA encoded by the same vector system did not change the susceptibility of T29Kt1 cells to oncrasin-1. Immunofluorescent analysis showed that knockdown of PKC\(_{L}\) in T29Kt1 cells abolished the abnormal aggregation of nuclear PKC\(_{L}\) (Fig. 5B), consistent with the results observed in T29 cells. Together, those results indicated that oncrasin-1 has synthetic lethality for PKC\(_{L}\).

**Antitumor activity in vivo.** We also investigated the in vivo antitumor activity of oncrasin-1. For this purpose, 1.5 \times 10^6 H460 cells were inoculated into the dorsal flank of each nude mouse. After the tumors grew to 2 to 3 mm in diameter, the mice were treated with i.p. injections of oncrasin-1 for 10 days at a dose of 100 mg/kg/injection daily, or they were given i.p. injections of solvent alone. The tumor volumes were monitored every other day. Blood samples were collected from the tail vein before treatment and 2 days after the last treatment for testing of serum liver enzymes. The results showed that, in comparison with solvent, oncrasin-1 suppressed tumor growth by 75.4% (Fig. 6A). Treatment with oncrasin-1 also prolonged survival (Fig. 6B): the mean survival times for mice treated with solvent and oncrasin-1 were 24 and 32, respectively. No differences were observed in the body weights of mice treated with solvent or oncrasin-1. In addition, the serum alanine aminotransferase, aspartate aminotransferase, and creatinine levels were within the reference ranges in all mice tested, regardless of the treatment received, suggesting that in vivo antitumor activity can be achieved without observable toxicity.
Those data showed that oncrasin-1 might be useful for the treatment of cancers with K-Ras mutations.

**Discussion**

Synthetic lethality was originally called a lethal phenotype caused by mutations of two genes (19); i.e., mutations of the two genes are viable if they occur separately, but if they occur together, the combination is lethal. A synthetic lethal phenotype often indicates that the two genes or two related pathways affect a common essential biological function. Assume that the biological event E, which is critical for the cell to survive, is affected by signals A and B. Signal A is transduced via proteins A1, A2, and A3, whereas signal B is transduced via B1, B2, and B3 and then to E. An abnormality occurring in either signal pathway is insufficient to cause dysfunction of E; therefore, cell is viable. However, abnormalities in both signal pathways lead to the disorder of E and thus to cell death. In this case, A1 is synthetic lethal with B1, B2, or B3 but not with A2 or A3, and vice versa. Nevertheless, our current knowledge of molecular networks in normal or cancer cells is not adequate for us to predict what genes are synthetic lethal to an oncogene. The advantage of synthetic lethality screening is that a compound targeting to a protein that is synthetic lethal to an oncogenic protein can be identified, without prior knowledge of such a protein target. The disadvantage of this approach is that identifying targets of such a compound remains challenging. On the basis of our results, we hypothesize that oncrasin-1 affect some cellular targets that share an essential biological function with the K-Ras/PKC<sub>i</sub> pathway. Oncrasin-1 may not function by inhibition of K-Ras or PKC<sub>i</sub> activities but require K-Ras or PKC<sub>i</sub> activity for its apoptosis induction in cancer cells because it did not inhibit PKC<sub>i</sub> activity in an *in vitro* enzyme assay with recombinant PKC<sub>i</sub> protein nor inhibit S<sup>35</sup>-GTP<sub>y</sub> binding to K-Ras (data not shown), and because the siRNAs of K-Ras and PKC<sub>i</sub> induced an antagonistic but not an additive effect with oncrasin-1. Although the direct target or targets of the oncrasin-1 remain to be characterized, our results led us to hypothesize that it affects some cellular targets whose reduced or enhanced activity is lethal for cancer cells with increased K-Ras and/or PKC<sub>i</sub> activity. In fact, oncogenic Ras can induce either cell transformation or apoptosis, depending on cell types and contexts (20, 21). Expression of oncogenic Ras in primary human or rodent cells often results in apoptosis or senescence, whereas expression of oncogenic Ras in immortal cells or cells with inactivation of p53, p16, or the transcriptional activator IFN regulatory factor 1 leads to transformation and tumorigenesis (20, 21). It is possible that, in comparison with cancer cells, the cellular targets of oncrasin-1 in primary cells are at hypostatus or hyperstatus that is not viably compatible with increased K-Ras/PKC<sub>i</sub> activity.
K-Ras mutations are frequently found in various types of human cancer and often associated with resistance to radiotherapy and chemotherapy, including novel anticancer agents such as cetuximab and erlotinib (22). As a result, the outcome for cancer patients with K-Ras mutations is frequently poor (23). Similarly, poor outcomes have recently been observed in cancer patients with overexpression of PKCζ (24, 25). Unlike other protein kinase C, PKCζ and PKCs are insensitive to regulation by diacylglycerol, Ca²⁺, or phorbol esters but are activated by phosphorylase b-3-phosphate (33). A recent study showed downstream effectors, mediating signal transduction in certain of the aPKCs (32). Thus, the aPKCs might function as Ras regulators by phosphoinositides (28). Ras directly interacts in a GTP-dependent manner with the catalytic subunit of the PI3Ks and activates them (29, 30), leading to the generation of a short-lived second-messenger substrate for PKCζ and to the activation of many PI3K/PDK1-dependent kinases, including aPKCs (27) and Akt (31). Moreover, Ras proteins can directly interact with aPKCs in vivo and in vitro, regulating the activities of the aPKCs (32). Thus, the aPKCs might function as Ras downstream effectors, mediating signal transduction in certain important Ras signaling pathways (33). A recent study showed that PKCζ is required for K-Ras-induced transformation and colonic carcinogenesis in vivo (34). Nevertheless, how K-Ras and PKCs interact and what signal transduction they mediate remain to be characterized. Our study showed that treatment with oncrasin-1 led to aggregation of nuclear PKCs into large foci. Whether this abnormal PKCζ aggregation is related to oncrasin-1-induced apoptosis is not yet clear, although this phenotype is only observed in sensitive cells. Because of the critical roles of increased K-Ras/PI3Kζ activity in oncogenesis and in the poor outcome of cancer patients (23, 25), oncrasin-1 or its analogues that can induce synthetic lethality with oncogenic K-Ras and PKCs can be useful agents for cancer treatment or useful tools for characterizing biological functions of oncogenic K-Ras and PKCs, although the direct targets of oncrasin-1 are not yet clear.

Disclosure of Potential Conflicts of Interest

W. Gao, S. Wu, J. Liu, and B. Fang are all listed as co-inventors on patent filed by M. D. Anderson Cancer Center.

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References

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