Enhanced Cell Killing Induced by the Combination of Radiation and the Heat Shock Protein 90 Inhibitor 17-Allylamino-17-Demethoxygeldanamycin: A Multitarget Approach to Radiosensitization

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ABSTRACT

Purpose: Current strategies for tumor cell radiosensitization focus on a target-based approach. However, the radioresponse of a tumor cell is influenced by a wide variety of signaling molecules existing in a number of different survival pathways. Therefore, in an attempt to increase the probability and/or degree of radiosensitization, we have begun to investigate a multitarget approach using the heat shock protein 90 inhibitor 17-allylamino-17-demethoxygeldanamycin (17AAG).

Experimental Design: The effect of 17AAG on the levels of three proteins (Raf-1, ErbB2, and Akt) previously implicated in the regulation of radiosensitivity was determined in four human tumor cell lines. Tumor cell survival after exposure to corresponding concentrations of 17AAG combined with clinically relevant doses of X-rays was then evaluated using a clonogenic assay. The radiosensitivities of a nonimmortalized, normal fibroblast cell line was also determined after exposure to 17AAG.

Results: Exposure to nanomolar concentrations of 17AAG reduced the levels of the three radiosensitivity-associated proteins in a cell type manner. Using corresponding concentrations, 17AAG enhanced the radiosensitivities of each of the tumor cell lines with enhancement factors ranging from 1.3 to 1.7. The enhancement appeared to be related to the number of radioresponse-regulatory proteins affected. In contrast to the tumor cell lines, 17AAG had no effect on the radiosensitivity of a normal, nonimmortalized human fibroblast cell line.

Conclusions: These data suggest that heat shock protein 90 may be an appropriate target for selectively enhancing the radiosensitivity of tumor cells over normal cells. Furthermore, they illustrate the potential of a multitarget approach to radiosensitization.

INTRODUCTION

Recent investigations have demonstrated that a variety of signal transduction pathways can act to enhance tumor cell survival after exposure to ionizing radiation. Accordingly, a number of studies have reported that inhibiting a specific molecular component of a given radiation-activated signaling pathway can result in a decrease in the survival response and, consequently, an increase in tumor cell radiosensitivity. However, the ability of a specific molecule to influence radioresponse often depends on the genetic background of the tumor cell. For example, inhibition of Raf-1, Wee1, or nuclear factor kB activity (1–3) has been shown to enhance the radiosensitivity of some but not all tumor cells. Moreover, the abnormal signaling pathways of tumor cells can mediate the expression of multiple survival responses, each of which may influence radiosensitivity (4).

Given the potential limitations of focusing on an individual molecule or pathway, it would appear that targeting multiple radioresponse pathways simultaneously should lead to more effective radiosensitization. One strategy for such a multitarget approach to radiosensitization is to use an agent directed against the molecular chaperone Hsp90. Hsp90 is involved in mediating cellular response to stress and has a relatively high selectivity for proteins involved in signal transduction (5). Among the client proteins of Hsp90 are steroid hormone receptors, Src family kinases, Cdk (Cdk4 and Cdk6), and the hypoxia inducible factor-1α transcription factor (5). In addition, Hsp90 acts to stabilize Raf-1, Akt, and ErbB2 (5), each of which has been associated with protection against radiation-induced cell death, and a reduction in their individual activities results in radiosensitization (1, 6, 7).

As a means of inhibiting Hsp90 function, initial laboratory studies focused on radicicol and geldanamycin; however, these compounds were found to have excessive toxicity when delivered in vivo (5). In contrast, the geldanamycin analogue 17AAG retains the antitumor effects of geldanamycin with significantly...
less toxicity and has recently entered clinical trials (8). Therefore, to investigate Hsp90 as a potential target for tumor cell radiosensitization, we have evaluated the effects of 17AAG exposure on the levels of the radioreponse-regulatory proteins Raf-1, Akt, and ErbB2 and on the radiosensitivity of four human tumor cell lines.

MATERIALS AND METHODS

Cell Lines and Treatment. Four human tumor cell lines were evaluated: two gliomas (U251 and SF539) and two prostate carcinomas (DU145 and PC3), which were obtained from American Type Culture Collection (Manassas, VA). Each cell line was grown in RPMI 1640 (Life Technologies, Inc., Rockville, MD) containing 5 mM glutamate and 5% fetal bovine serum and maintained at 37°C in an atmosphere of 5% CO₂ and 95% room air. The nonimmortalized normal human fibroblast cell line C-29A (provided by Dr. W. A. Brock; The University of Texas M. D. Anderson Cancer Center, Houston, TX) was grown in DMEM containing gentamicin (10 μg/ml), 20% fetal bovine serum, and 2 mM glutamine. This fibroblast cell line was initiated from normal skin and used for experiments in passages 1 and 4. 17AAG, provided by the Division of Cancer Treatment and Diagnosis of the National Cancer Institute, was dissolved in DMSO to a stock concentration of 10 mM and stored at -20°C. Cultures were irradiated using a Pantak (Solon, OH) X-ray source at a dose rate of 1.55 Gy/min.

Clonogenic Assay. Cultures were trypsinized to generate a single cell suspension, and a specified number of cells were seeded into each well of 6-well tissue culture plates. After allowing cells time to attach (4 h), 17AAG or DMSO (vehicle control) was added at specified concentrations, and plates were irradiated 24 h later. Immediately after irradiation, DMSO or 17AAG-containing media were aspirated, and fresh media were added. Twelve to 14 days after seeding, colonies were stained with crystal violet, and the number of colonies containing at least 50 cells was determined, and the surviving fractions were calculated. Radiosensitivity was quantified according to the MID, representing the area under the curve (9). The effects of 17AAG on radiosensitivity were expressed as the RER, defined as (MID of control group)/(MID of treatment group).

Immunoblot Analysis. Cell were exposed to 17AAG or vehicle control (DMSO) for 24 h, scraped into PBS, and centrifuged, and the cell pellet was resuspended in 3 volumes of lysis buffer [20 mM HEPES (pH 7.9), 400 mM NaCl, 1 mM EDTA, 1 mM EGTA, 1% NP40, 1 mM DTT, 1 mM phenylmethylsulfonyl fluoride, 1 mg/ml aprotinin, 1 mg/ml leupeptin, 250 mg/ml benzamidine, 50 mM NaF, and 1 mM NaOAc]. Immunoblot analysis was then performed as described previously by Russell et al. (3). The antibodies to cRaf-1, Akt, ErbB2, and Hsp90 were obtained from Santa Cruz Biotechnology (Santa Cruz, CA), and antibodies to actin were obtained from Chemicon (Temecula, CA.). Visualization and quantification were performed using the Typhoon scanner (Molecular Dynamics, Sunnyvale, CA).

Cell Cycle Phase Analysis. Evaluation of cell cycle phase distribution was performed using FCM. The treatment protocols were essentially the same as those in the clonogenic survival experiments, except that the cells were initially seeded into 10-cm dishes. All cultures were subconfluent at the time of collection. Cultures were collected for fixation, stained with propidium iodide, and analyzed using FCM as described previously (10) by the Clinical Services Program at National Cancer Institute-Frederick.

RESULTS

Four human tumor cell lines were used in this study: two prostate carcinomas (PC3 and DU145) and two gliomas (U251 and SF539). As an initial characterization of the response of each tumor cell line to 17AAG, survival curves were generated after a 24-h exposure period (Fig. 1). The cell lines had different sensitivities to 17AAG-induced cell death: PC3 was the most resistant; DU145 was the most sensitive; and the two glioma cell lines (U251 and SF539) had relatively intermediate sensitivity. Although most studies evaluating 17AAG as an antitumor agent have relied on proliferation as an end point, the results in Fig. 1 are consistent with the 17AAG concentrations previously reported to induce clonogenic cell death for two other glioma cell lines (11).

Immunoblot analysis was used to determine the levels of the radioreponse-regulatory proteins Raf-1, Akt, and ErbB2 in each cell line after 24 h of 17AAG exposure (Fig. 2). In SF539 cells, there was a concentration-dependent decrease in the levels of Raf-1, Akt, and ErbB2 beginning at approximately 50 nM, with each reduced by >50% after exposure to 75 nM 17AAG. Similar results were obtained for U251 cells, except that at 25 nM 17AAG, ErbB2 levels were significantly reduced, although Raf-1 and Akt levels were unaffected. PC3 cells were the least sensitive to 17AAG according to the cell survival analyses (Fig. 1), and a similar ranking was found for changes in protein levels. Raf-1 and ErbB2 levels were reduced by >50% at 75 and 100 nM 17AAG, but Akt levels remained unchanged to at least 100 nM 17AAG. The most sensitive of the four cell lines to 17AAG was DU145, in which significant reductions in Raf-1, ErbB2, and Akt were detected at 50 nM 17AAG. In addition,
ErbB2 levels were significantly reduced in response to 10 nM 17AAG, although Raf-1 and Akt were unaffected at this dose. In each of the cell lines, the levels of Hsp90 were unaffected over the 17AAG concentrations evaluated, consistent with previous results (11, 12). Although there is some cell type dependency, the 17AAG-mediated decreases in Raf-1 and ErbB2 levels detected in these four cell lines are, for the most part, consistent with previous reports using other cell types (13–15). As reported previously, Akt levels appear to be the most resistant to 17AAG (13, 15).

To determine whether 17AAG enhances tumor cell sensitivity to radiation-induced cell death, cell lines were exposed to 17AAG (24 h) and irradiated, and the colony-forming efficiency assay was performed. Radiation survival curves (Fig. 3) were generated for each cell line after normalization for the level of cell killing induced by 17AAG alone. For each cell line, two concentrations of 17AAG were evaluated: (a) one that reduced survival to approximately 30%; and (b) a lower concentration that reduced the surviving fraction to ≥60%. In addition, these two concentrations of 17AAG had different effects on the three radioresistance-associated proteins evaluated in Fig. 2. As shown in Fig. 3A, pretreatment of SF539 cells with 75 nM 17AAG resulted in a significant decrease in cell survival as compared with radiation only (RER = 1.7). At this 17AAG concentration, the levels of all three putative radioresponse regulatory proteins were changed. When SF539 cells were exposed to a concentration of 17AAG that did not affect any of the three proteins (25 nM) but did reduce survival to 60% (Fig. 1), no significant increase in radiosensitivity was detected (RER = 1.1). Exposure of U251 cells to a concentration of 17AAG (75 nM) that modified all three proteins also resulted in a significant enhancement in radiation-induced cell killing (RER = 1.6). Treatment of U251 cells with 25 nM 17AAG, which only affected ErbB2 levels, also enhances cell killing, but not to the extent detected after the higher concentration (RER = 1.3). PC3 cells were the most resistant to 17AAG and were treated with 100 nM 17 AAG before irradiation. At this concentration, although Raf-1 and ErbB2 levels were reduced, no change in Akt levels was detected, which was unique to this cell line. As shown in Fig. 3C, pretreatment with 100 nM 17AAG enhanced the radiosensitivity of PC3 cells (RER = 1.4), whereas exposure to 25 nM 17AAG had no effect on radiation-induced cell death (RER = 1.0). DU145 cells were the most sensitive of the four cell lines with respect to cell killing and protein changes induced by 17AAG. Using a concentration of 50 nM 17AAG, which reduced each of the three radioresistance-associated proteins, a significant radiosensitization was induced (RER = 1.6). Exposure of DU145 cells to 10 nM 17AAG, which only affected...
ErbB2 levels, also enhanced radiosensitivity, but to a slightly smaller degree (RER = 1.5). Thus, these data indicate that 17AAG exposure results in an enhanced radiosensitivity of each of the four human tumor cell lines evaluated.

Exposure of some human colon adenocarcinoma cell lines to 17AAG has been reported to result in an accumulation of cells in the G2-M phases on the cell cycle (13). Because such an effect can be a critical parameter in determining radiosensitivity, FCM was used to determine the cell cycle phase distribution of the tumor cell lines after exposure to their respective radiosensitizing concentrations of 17AAG. As shown in Table 1, after 24 h of 17AAG exposure (the time of enhanced radiation-induced cell killing), the cell cycle phase distribution patterns for each of the cell lines were similar to those for cultures receiving vehicle only. These results indicate that redistribution of cells into a radiosensitive phase of the cell cycle does not account for the 17AAG-mediated enhancement in radiation-induced cell killing. It should be noted that the 17AAG concentrations used to enhance radiosensitivity in this were ≈100 nM, whereas the concentrations that affected the cell cycle distribution of the colon tumor cell lines was ≈1 μM (13).

The therapeutic potential of 17AAG as a radiation modifier will ultimately depend on a selective increase in the radiosensitivity of tumor cells over normal cells. To begin to address this potential, we have evaluated the effects of 17AAG on the radiosensitivity of the nonimmortalized, normal human diploid fibroblast cell line C29-A. The treatment protocol was the same as that used for the tumor cell lines. Monolayer cultures of exponentially dividing C29-A cells were exposed to 75 nM 17AAG for 24 h and irradiated, and the clonogenic survival was determined. It should be noted that the radiosensitivity of C29-A cells is considerably greater than that of the tumor cell lines (compare control survival curves in Figs. 3 and 4). This enhanced sensitivity of C29-A (or resistance of the tumor cell lines) is consistent with a previous report showing that nonimmortalized, normal human fibroblast cell lines are generally more sensitive than tumor cell lines (16). Treatment of C29-A cells with 17AAG only reduced the surviving fraction to 0.80 ± 0.01. In contrast to the results obtained from the tumor cell lines, treatment of C29-A cells with 17AAG had no effect on radiation-induced cell killing (Fig. 4). To begin to investigate the selective sensitization of the tumor cells, the levels of Hsp90,

Table 1  Effect of 17AAG on cell cycle phase distribution

Tumor cell lines were exposed to control vehicle (C) or a radiosensitizing concentration of 17AAG (U251, 75 nM; SF539, 75 nM; PC3, 100 nM; DU145, 50 nM) for 24 h (T). Cells were then collected and processed for FCM for determination of cell cycle phase distribution.

<table>
<thead>
<tr>
<th></th>
<th>U251</th>
<th>SF539</th>
<th>PC3</th>
<th>DU145</th>
</tr>
</thead>
<tbody>
<tr>
<td>% G1</td>
<td>46.8</td>
<td>54.9</td>
<td>33.1</td>
<td>28.2</td>
</tr>
<tr>
<td>% S</td>
<td>23.5</td>
<td>21.2</td>
<td>20.0</td>
<td>25.4</td>
</tr>
<tr>
<td>% G2-M</td>
<td>24.0</td>
<td>15.5</td>
<td>39.1</td>
<td>36.7</td>
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</tbody>
</table>

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the initial target of 17AAG, were determined. As shown in Fig. 5, the tumor cell lines contain 2–3 times more Hsp90 than the normal fibroblasts. Exposure to 17AAG had no effect on the Hsp90 levels in each of the cell lines (data not shown). Immuno- blot analyses showed that exposure of C29-A cells to 17AAG reduced the levels of Akt, ErbB2, and Raf-1 to a similar degree as detected after treatment of the tumor cell lines. Whereas the reduction of these proteins after 17AAG exposure is consistent with an inhibition of Hsp90, the failure of 17AAG to enhance the radiosensitivity of C29-A cells suggests that Raf, Akt, and ErbB2 do not play a role in regulating the radiosponse of this normal cell line.

**DISCUSSION**

Attempts to develop clinically relevant radiosensitizers have traditionally used an empirical approach combining radiation with standard cytotoxic chemotherapeutic agents. Although often effective in experimental models, the results obtained when these combinations are applied in a clinical setting have generally been less than expected. Recently, arising from an increased understanding of the molecular mechanisms of radioresponse, attempts to increase tumor radiosensitivity have begun to use a target-based approach. However, the radioresponse of a cell is influenced by a wide variety of molecules existing in a number of different survival pathways; consequently, there are multiple targets available that can affect tumor cell radiosensitivity. Whether a target has a major, minor, or no role in determining radioresponse will be subject to at least some degree of cell type specificity. Given the heterogeneity that exists within solid neoplasms, the significance of a single target with respect to radiosensitivity is likely to vary even among the cells of an individual tumor. Thus, the ability to affect more than one radioreceptor-regulatory molecule should offer advantages in terms of the probability of enhancing radiosensitivity. Furthermore, multiple survival pathways, such as prolonged G2 arrest, enhanced DNA repair capacity, and limited apoptosis can be operative within a tumor cell (4), each potentially contributing independently to radioresistance. In this setting, attenuating more than one survival pathway should lead to a greater degree of sensitization.

In an attempt to address the potential limitations imposed by cell type specificity and multiple survival pathways, we have begun to investigate a multitarget approach to tumor cell radiosensitization using the Hsp90 inhibitor 17AAG. As reported for other cell lines (13, 17), exposure of the four human tumor lines evaluated here to 17AAG only was 0.80 ± 0.01.
tions in three proteins associated with radiosensitivity (Raf-1, ErbB2, and Akt). Consistent with a role for these proteins in radiosensitivity, the same 17AAG exposure protocols induced a significant increase in the radiosensitivity of four of the four human tumor cells evaluated, with RERs ranging from 1.3 to 1.7. Although concentration dependent, the 17AAG-mediated enhancement in radiation-induced cell killing occurred in both prostate carcinoma and glioma cell lines. Given that these cell lines are of diverse genetic backgrounds including differences in p53 gene mutational status (18), these data are suggestive of a general ability of 17AAG to enhance radiosensitivity.

Although evidence is available indicating that individual reductions in Raf-1, Akt, and ErbB2 can result in tumor cell radiosensitization, there are also data indicative of cell type specificity. For example, exposure to an antisense raf oligodeoxyribonucleotide resulted in the radiosensitization of some but not all of the human tumor cell lines evaluated (1). With respect to Akt, Gupta et al. (6) reported that inhibition of phosphatidylinositol 3'-kinase activity leading to a reduction in activated Akt resulted in the radiosensitization of cells containing mutant but not wild-type ras genes. Furthermore, Tezuka et al. (19) showed that in another tumor cell model, reducing active Akt through inhibition of phosphatidylinositol 3'-kinase had no effect on radiosensitivity. Finally, treatment of human breast cancer cells that overexpress ErbB2 with an antibody directed against the receptor was shown to result in radiosensitization (7). However, whereas each of the cell lines investigated herein expresses ErbB2, there is considerable heterogeneity in ErbB2 expression in tumor cells in general (20, 21), which would be an obvious limitation as a target for radiosensitization. Thus, as targets for a radiosensitizing agent, each of these proteins would suffer from a potential for cell type specificity. However, if it is assumed that at least one of these radiosensitive-regulatory proteins would be operative in a majority of cells, then targeting all three should significantly increase the likelihood of enhancing a given tumor cell’s radiosensitivity.

Whereas it can be speculated that the radiosensitization induced by 17AAG involves one or more of the proteins evaluated (Raf-1, Akt, or ErbB2), based on the results presented it is not possible to establish a specific causal relationship between the reduction in one of these proteins and the enhancement in radiosensitivity. Clearly, the delineation of the molecular process responsible for the 17AAG-mediated enhancement in radiosensitivity will be complicated by potential changes in the levels of each of the Hsp90 client proteins. Moreover, the specific mechanism of radiosensitization may depend on the 17AAG dose. As illustrated by U251 and DU145 (Fig. 3), the lower 17AAG dose evaluated in the radiation survival studies (25 and 10 nM, respectively) resulted in only the loss of ErbB2, yet did enhance radiosensitivity. These results suggest that ErbB2 plays a critical role in the radioreistance of these tumor lines. However, higher concentrations of 17AAG (75 and 50 nM for U251 and DU145, respectively) did not further reduce ErbB2 levels but did result in decreases in Raf-1 and Akt proteins and induced relatively higher degrees of enhancement, which suggests that more than one mechanism may be operative. Along these lines, previous reports have suggested that, although the mechanism for Raf-mediated radioreistance has not been defined, ErbB2 acts to enhance DNA repair (7), and Akt acts to reduce apoptosis (22). Attenuating the levels of each of these proteins should then target a distinct survival pathway that contributes to radioresistance.

Critical to a favorable therapeutic ratio, 17AAG had no effect on the radioresistance of a normal, nonimmortalized human fibroblast cell line. This is encouraging with respect to potential clinical applications, that is, at the same treatment dose, 17AAG enhances the radioresistance of tumor cells without sensitizing normal cells. The mechanism responsible for this selective sensitization of tumor cells over normal cells, however, remains unclear. 17AAG reduced the levels of the radioresistance-associated proteins Raf, Akt, and ErbB2 in C29-A cells, as it did in the tumor cell lines, however, in this cell line these decreases were not accompanied by an increase in radiosensitivity. This lack of correlation between the reduction in these proteins and an enhancement in radiation-induced cell killing might be explained by C29-A’s normal cell status and concomitantly significantly greater degree of radioresistance as compared with the tumor cell lines (Figs. 3 and 4). In a comparison of the in vitro radiosensitivity of a wide variety of cell lines, Deschavanne and Fertil (16) reported that nonimmortalized, normal cells are, in general, considerably more sensitive than tumor cells. Along these lines, it had been suggested that the difference in radiosensitivity between normal and tumor cells is the result of the activation of radiation resistance pathways by the oncogenic transformation process (23). More recent studies have also shown that the overexpression of a variety of oncogenic tyrosine kinases enhances cellular resistance to DNA-damaging agents (4). It can be assumed that the oncogenic-mediated resistance pathways are not operative in the normal C29-A cells, consistent with their enhanced radioresistance. Thus, in C29-A cells, the 17AAG-induced reduction in proteins involved in oncogenic-mediated radioresistance in tumor cells, presumably including Raf, Akt, and/or ErbB2 (1, 6, 7), would not be expected to further increase their already high degree of sensitivity. In other words, 17AAG acts to compromise the radioresistance pathways in tumor cells; because these pathways do not exist in normal cells, 17AAG has no effect on their radiosensitivity. Clearly, this remains speculation and will be subject to further investigation.

This is the initial investigation into a multitarget approach to radiosensitization, and clearly more studies are required. However, results of this study indicate that 17AAG significantly enhances radioresitivity of four human tumor cell lines and that this enhancement corresponds with the reduction of a protein or proteins associated with radioresistance. Whereas they cannot be technically designated as targets, these proteins could serve as markers for 17AAG action in vivo necessary to optimize its combination with radiation. For example, Solit et al. (15) recently reported a decrease in ErbB2 levels in a prostate carcinoma xenograft model after 4 days of 17AAG treatment; the ErbB2 levels then recover after the cessation of drug delivery. These results suggest that whereas 17AAG alone will primarily be cistostatic in vivo, if radiation were to be delivered during the window of ErbB2 reduction, there could be an enhancement in radiosensitivity and consequently, an increase in antitumor effectiveness. Although complicated on a fundamental mechanistic level, the translation of 17AAG to a treatment situation in combination with radiotherapy may be of
potential benefit. That is, by targeting multiple proteins that can mediate tumor cell radioresistance, the application of 17AAG or similar agents could result in an increase in the probability and degree of radiosensitization.

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REFERENCES


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