In Vitro Effects of N,N-Dimethylformamide on Sublethal and Potentially Lethal Damage Recovery Processes after X-Irradiation in Heterogeneous Human Colon Tumor Cells

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ABSTRACT

The responses of unfed plateau-phase cultures of two clonal subpopulations of cells (clones A and D) from a human colon adenocarcinoma (DLD-1) to X-irradiation were examined in detail either as control cultures or after growth in medium containing the differentiating agent N,N-dimethylformamide (DMF, 0.8%, three passages). Specifically, the cultures were studied with regard to their ability to express both potentially lethal and sublethal damage recovery (PLDR and SLDR, respectively). In PLDR studies on control cells, clone D expressed more PLDR than clone A, although recovery half-times were the same. DMF treatment increased the expression of PLDR in both cell lines and decreased the half-times for recovery. When recovery from sublethal radiation injury was assessed, the rate and extent of SLDR in non-DMF-treated clone A and D cells were identical. In contrast to the PLDR results, DMF treatment had no significant effect on SLDR in either cell line. These studies show that, while DMF treatment of human colon tumor cells increases cell killing in the clinically relevant, low-dose ("shoulder") region of the X-ray survival curve, this increase in cytotoxicity is not due to an inhibition of the repair of sublethal damage.

INTRODUCTION

In a number of recent publications, we have clearly demonstrated the existence of significant intrinsic cellular tumor heterogeneity as shown by responses of individual subpopulations from both rodent and human neoplasms to cytotoxic agents such as drugs, hyperthermia, and ionizing radiation (Footnotes 3–5, Refs. 1–3 and 4–6). However, definitive evaluation of the importance of cellular neoplastic diversity to cytotoxic treatment specifically requires that not only should the single dose survival responses of various tumor subpopulations be described, but also that cellular repair and recovery processes operating after induction of damage be determined, because these processes play a vital role in the ultimate response to therapy. In the field of radiation biology, two posttreatment recovery processes have been well described. SLDR is a very important process, particularly for the low doses given in conventional multifraction radiation therapy, and is usually described by the width of the "shoulder" on a cellular dose-response curve. PLDR is a phenomenon usually seen at high doses and is characterized by changes in the final exponential slopes of dose-response curves (7). Both recovery processes (as well as the magnitude of intrinsic radiation resistance per se) will impact strongly on the radiocurability of tumors, but to our knowledge, no data on posttreatment recovery processes as they exist in the context of heterogeneous neoplasms have yet been published.

In addressing approaches that might lessen the problem of intraneoplastic diversity, we and others (8, 9) have suggested that one might minimize diversity via the induction of a more differentiated state in cancer cells by treatment with certain chemical agents (i.e., N,N-dimethylformamide, N-methylformamide, dimethyl sulfoxide, sodium butyrate, retinoic acid, hexamethylene-bisacetamide, etc.). The rationale for this suggestion is that such treatment might serve to homogenize a heterogeneous tumor by decreasing the variability in responsivity among tumor subpopulations that is routinely documented (8). Recently, in studies in which such "maturational or differentiation" therapy was combined with treatment using classical cytotoxic agents such as cis-platinum or ionizing radiation, a decrease in the extent of variability of response and an enhancement of the sensitivity of the tumor cells were observed (Footnote 7; Refs. 10–15). Consequently, we have suggested that such differentiating agents could be combined with appropriate cytotoxic agents in the strategy of therapy of heterogeneous tumors.

To date, the combination of differentiation-inducing chemicals with other agents such as X-rays has involved studies in which only single graded doses of the agents were used on exponentially growing cells (Footnote 7; Ref. 10). This study was therefore undertaken to define how prior exposure of human colon tumor cells to the differentiating agent N,N-dimethylformamide might modify the processes of sublethal damage recovery and PLDR in two subpopulations from a heterogeneous tumor after X-irradiation.

MATERIALS AND METHODS

Human Tumor Cell Lines. The cell lines used in this work were two tumor subpopulations, termed clones A and D, originally isolated from a...
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heterogeneous human colon adenocarcinoma designated DLD-1. The cultivation and characterization of the DLD-1 system, as well as the isolation of the A and D subpopulations, have been previously described in detail (Footnotes 3 and 7; Refs. 1 and 14). In our laboratory, these tumor cell lines are maintained in RPMI 1640 supplemented with 10% fetal calf serum, buffers, and antibiotics (13). Stock cultures are passaged twice weekly and are maintained in 25-cm² plastic flasks (Falcon Plastics, Oxnard, CA). Cell lines are replaced from frozen stocks every 6 mo. At the time of replacement of cultures, basic growth characteristics and radiation responses are redetermined to assure phenotypic response stability of the tumor lines.

**Treatment of Colon Cancer Cells with DMF.** Cells were exposed to 0.8% DMF (v/v; Sigma Chemical Company, St. Louis, MO) in RPMI 1640. This concentration was based on previously published data indicating that, at 0.8% DMF, essentially maximal differentiation effects had been achieved (8, 10, 11, 13-15). Cells were cultured in the presence of DMF for three passages prior to the start of X-ray experiments. Under these conditions, the plating efficiency of these cells was the same as control cells, 40-50%. Cells were always irradiated in the presence of DMF-containing medium and were replated into complete medium without DMF after the irradiation and recovery period for subsequent colony formation. We have previously demonstrated that DMF added to non-DMF-treated cells immediately before X-irradiation does not modify the shape of the resultant survival curve (13) (e.g., by chemical scavenging of free radicals).

**In Vitro Growth Curves.** To determine cell culture doubling times, in vitro growth curves were carried out according to standard techniques (13). As all the subsequent X-ray experiments were to be done on unfed plateau-phase cultures, no medium changes were performed after the initial seedings. Cell counts were obtained daily from three separate flasks and were counted using a Model 2Z Coulter Counter (Coulter Electronic Co., Hialeah, FL). Cell counts were plotted as a function of time, and cell culture doubling times were calculated from the linear portion of the growth curves.

**X-Irradiation Procedures.** For radiation survival experiments, exposures of flasks were done at ambient temperature, using a Picker X-ray machine operated at 100 kVp and 10 mA. The target-to-sample distance was 15.2 cm with 1 mm of aluminum as added filtration. Exposure doses were measured with an R-meter (Victoreen Instrument Co., Cleveland, OH) and converted to absorbed doses using a R-to-Gy conversion factor of 0.0096 with appropriate temperature and pressure conversion factors. Dose rates were approximately 5.4 Gy/min (1 Gy = 100 rads).

**Survival Curve Studies.** For cell survival studies, unfed monolayer cultures of either DMF-treated or untreated cells were exposed in plastic flasks containing 5 ml of medium. Immediately after irradiation (immediate assay) or after 12 h at 37°C (delayed assay), the medium was removed, and the cells were detached with 0.05% trypsin-EDTA (GIBCO). After counting, cells were seeded at appropriate concentrations in 60-mm plastic Petri dishes (Falcon). Ten dishes at two different dilutions were seeded from each flask at each dose point, and experiments were replicated at least 3 times. Dishes were incubated at 37°C for 11-14 days until treated and untreated colonies were the same size, at which time colonies were stained with a 0.5% solution of crystal violet in absolute methanol. Colonies of 50 or more cells were scored as survivors.

**Data Analysis of Survival Curve Studies.** Data analysis on the survival curve studies was done by combining the data from individual experiments. A least-squares linear regression analysis was performed on the survival (S) curve data using the logarithms of the individual survival values from all the experiments versus the dose given for survival levels below 10%. The regression line was used to obtain values of D₀. The D₀ and n values were determined by the intersection of the regression line with the 100% survival line and with the abscissa (zero dose intercept), respectively. The 95% confidence limits on D₀ were obtained using standard statistical methods (16, 17).

**Recovery from Potentially Lethal Damage.** The experiments designed to investigate recovery from potentially lethal damage were performed using cells grown to saturation density (Days 7 and 8 for clone A control and DMF-treated cells, respectively, and Days 8 and 12 for clone D control and DMF-treated cells). These days were chosen so all cultures would be at the same stage of growth. The cultures were given a dose calculated to reduce survival to approximately 1% in all conditions. Immediately after irradiation, the flasks were returned to the incubator, and at various times postirradiation, the cells were detached, counted, and seeded into 60-mm dishes. The kinetics and magnitude of recovery were assessed by comparing the survival levels as a function of time to the survival when the irradiated cells were immediately subcultured for colony formation.

**Data Analysis for PLDR Studies.** Data analysis was done by combining data from at least three experiments. The absolute surviving fraction of cells at any time postirradiation was normalized to the survival seen immediately after irradiation. This normalized value was termed S. The recovery half-times (τₐₚ) were calculated using the accumulation of damage model of Roesch (18), in which a linear regression can be performed on the values obtained from the following ratio:

\[
\text{Maximum survival (S_max)} - \text{the observed survival at any time (S_t)}
\]
\[
S_{\text{max}} - \text{the survival at } t = 0 (S_{0})
\]

versus time postirradiation for time points up to 6 h. This function is linear up to 6 h, at which time the recovery curve begins to plateau. S_max was defined as the survival seen at 12 h postirradiation. The 95% confidence limits were calculated on this repair time by standard methods (17).

**Recovery from Sublethal Damage (Kinetic Studies).** Split-dose experiments were performed to investigate recovery from sublethal damage. Plateau-phase cultures of DMF-treated or untreated clone A and clone D cells were irradiated as described previously. The first dose delivered was calculated to reduce survival to 1%. After irradiations, all except the flasks replated immediately after irradiation (t = 0) were immediately returned to the incubator. At various times thereafter, flasks were removed from the incubator and given a second dose of X-rays to a combined total dose of 8.0 Gy. After the second dose, cells were detached, counted, and seeded for colony formation. As these experiments exhibit postirradiation survival occurring as a consequence of both PLDR and SLDR processes, the survival values obtained from the PLDR studies are subtracted from each time point in the study to obtain survival levels that reflect increases in survival due to SLDR alone.

**Data Analysis of SLDR Studies.** Data analysis was carried out in a manner identical to that described for studies investigating PLDR.

**Complete Survival Curve Studies of SLDR.** Flasks containing plateau-phase cultures were irradiated with a dose calculated to reduce survival to 1% and then returned to the incubator. At f = 0, a full survival curve was carried out as described previously. At f = 3, 6, and 12 h, flasks which had been irradiated previously were irradiated again with graded doses of X-rays ranging from 0-4.5 Gy at 0.5-Gy intervals. After irradiation, the cells were detached, counted, and seeded for colony formation.

**FCM Studies.** To define cell cycle distributions, exponential (48 h) and unfed plateau-phase cultures of either control or DMF-treated clone A and clone D cells were examined by flow cytometry. To do this, cultures were trypsinized and resuspended in PBS (GIBCO). A second centrifugation and resuspension in PBS were then performed, and cells were diluted to a concentration of 1-1.5 × 10⁶/ml (5 ml total volume). This suspension was then quickly mixed with an equal volume of ice-cold 70% ethanol and gently vortexed. Fixed samples were then stored at 4°C until processed for FCM. DNA histograms were obtained with an EPICS V dual laser flow cytometer (Coulter Electronics, Hialeah, FL) using an argon laser (457.9-nm excitation wavelength; additional filtration used was a 495-nm long pass filter), after staining with ethidium bromide and mithramycin. Instrument fluorescent emission calibration was routinely done using 10-μm-diameter fluorescent plastic microspheres (Coul-
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RESULTS

Effects of DMF on Growth. The effects of 0.8% DMF on the growth of clone A and clone D cells are shown in Chart 1. First, it may be seen that DMF increases the cell culture doubling times by about 40–50%. As this increase in doubling time appears to be due to an elongation of time spent in all phases of the cell cycle (Footnote 8, Ref. 19), DMF treatment should not affect the distribution of cells through the cell cycle. The results of FCM studies are shown in Chart 2. It may be noted that there is an enrichment in the percentage of G1 cells for both clone A and clone D cells as cultures progress from the exponentially growing state to an unfed plateau state. For clone A, this enrichment is by about 25%, and for clone D, this is by about 30%. Concomitantly, there are decreases in the percentages of S- and G2 + M-phase cells (30 and 27% decreases in the percentage of S-phase cells for clone A and clone D cultures, respectively). Although the growth curves for all conditions do not bend over to a plateau before peeling of the cultures occurs, the observed enrichment in G1 cells is similar to that described by Drewinko et al. (20) for other stationary-phase human colon tumor cells.

Also in Chart 2, we have included values for unfed plateau-phase cultures of clone A and clone D cells treated chronically with the 0.8% DMF. It may be seen that the FCM percentages obtained are similar to those for non-DMF-treated clone A and clone D cultures. Although there is still a slight further enrichment in G1-phase cells as compared to control, unfed plateau cultures, these differences are not statistically significant.

Effects of DMF on Survival after X-irradiation. The survival responses of unfed plateau cultures of clone A and clone D tumor cells after X-irradiation are shown in Chart 3. It may be seen that DMF has modified the shoulder of the survival curve for clone A cells much more than that for clone D cells, as we have previously reported for exponential cultures (10). There has also been a modification of the slope of the survival curve for clone D that is not observed for clone A. Survival parameters are listed in Table 1.

Kinetic Studies on the Recovery of Unfed, Plateau-Phase Cells to Single Doses of X-irradiation (PLDR Studies). As stated previously, non-DMF and DMF-treated cultures of clone A and clone D cells were given single X-ray doses sufficient to reduce the immediate survival to about 1%. Then, as a function of time after exposure, cultures were assayed for survival, and the results of these studies are shown in Chart 4. Two features...
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Table 1
Survival curve parameters of human colon tumor cells from unfed, plateau-phase cultures after treatment with DMF and X-irradiation

| Tumor subpopulation          | $D_0$ (Gy) | $n$ | $D_0$ (Gy) | Correlation coefficient
|-----------------------------|------------|----|------------|------------------------
| Clone A (immediate assay)    | 2.23       | 16.8 | 0.79 ± 0.02$^a$ | 0.98$^c$ (33)         |
| -DMF                        |            |     |            |                        |
| +DMF                        | 1.21       | 4.09 | 0.86 ± 0.02 | 0.99$^c$ (29)         |
| Clone A (delayed, 12 h, assay)$^b$ | 2.20       | 15.3 | 0.81 ± 0.02 | 0.97$^c$ (18)         |
| -DMF                        |            |     |            |                        |
| +DMF                        | 1.26       | 4.22 | 1.42 ± 0.06 | 0.94$^c$ (22)         |
| Clone D (immediate assay)    | 2.42       | 31.3 | 0.70 ± 0.05 | 0.97$^c$ (35)         |
| -DMF                        |            |     |            |                        |
| +DMF                        | 1.74       | 6.46 | 0.94 ± 0.04 | 0.99$^c$ (30)         |
| Clone D (delayed, 12 h, assay)$^b$ | 1.54       | 4.06 | 1.11 ± 0.04 | 0.97$^c$ (26)         |
| -DMF                        |            |     |            |                        |
| +DMF                        | 1.51       | 3.09 | 1.34 ± 0.06 | 0.96$^c$ (24)         |

$^a$ The correlation coefficients of the linear regression fit of the data to define $D_0$ were determined (17).

$^b$ Mean ± SE.

$^c$ Statistically significant at the 0.05 level of confidence (17).

$^d$ Numbers in parentheses, number of data points used to determine the correlation coefficients.

$^e$ The delayed assay was performed 12 h after X-irradiation to assess the extent of PLDR and the effects of DMF thereon.

of these data are immediately apparent. (a) Intrinsic tumor heterogeneity is shown by the fact that clone D expresses more recovery from potentially lethal damage than does clone A. (b) DMF promotes PLDR in both tumor lines, albeit to a somewhat greater extent in clone D cells.

The recovery half-times for clone A are 4.5 ± 3.5 h (−DMF) and 2.3 ± 0.4 h (+DMF). Values for clone D are 4.1 ± 1.2 h (−DMF) and 1.8 ± 0.6 h (+DMF) (mean ± SE, 28). Therefore, non-DMF-treated unfed cultures of clone A and clone D cells have nearly the same $t_{1/2}$ values for PLDR. DMF treatment reduces these $t_{1/2}$ values by about 50% in clone A and about 56% in clone D, indicating an apparently faster PLDR process after DMF treatment. The correlation coefficients of the linear regression fitting used to determine the recovery half-times were determined, and these values were then tested for their significance (16). A strong linear correlation significant at the 1% level of confidence was found for all of the conditions investigated.

Chart 5 illustrates the nature of the changes in the survival curves when cells are assayed 12 h after irradiation for both non-DMF and DMF-treated cells. The major change has been an increase in the $D_0$ value of the survival curve for both experimental conditions as compared to those seen after immediate plating, and the actual survival parameters are listed also in Table 1.

Effects of DMF on Recovery from Sublethal X-Ray Damage. In these studies, non-DMF and DMF-treated cultures were given an initial X-ray dose sufficient to reduce immediate survival to about 1% (as in the PLDR studies), but they were then given graded second doses 3, 6, or 12 h later and assayed for survival as shown in Charts 6 and 7 for clone A and clone D cells, respectively.

In Charts 6 and 7, several features of the data may be described. (a) In all of the 3-, 6-, and 12-h postirradiation survival curves, the assayed survival curves express PLDR as shown by the vertical displacement in the survival of cells receiving no...
second dose irradiation (the 0 dose points on the graded second dose survival curve). As stated previously, this PLDR effect can be subtracted from the overall survival seen in these studies to examine the effects of DMF on SLDR alone. (b) If the PLDR effect is subtracted, there is no difference in the extent of SLDR between unfed cultures of clone A and clone D cells. The survival curve parameters of the recovery curves are listed in Table 2. (c) Further, DMF appears to have no effect on the recovery from sublethal radiation injury. This can be determined by comparing the survival curve parameters of the 3-, 6-, and 12-h split-dose curves (Table 2) and by examining the kinetics of recovery. The results of the kinetic studies are shown in Chart 8. It may be seen that the DMF treatment has had no significant effect on the rate of repair of sublethal damage. For both clone A and clone D, essentially complete repair occurs by 6 h postirradiation.

The half-times ($t_{50}$) for recovery from SLDR are, for clone A, 1.4 h ($-DMF$) and 1.6 h ($+DMF$), and for clone D, 1.6 h ($-DMF$) and 1.6 h ($+DMF$). These repair half-times are not statistically different.

**DISCUSSION**

These single dose and split dose studies on the responses of these two human colon tumor subpopulations to a specific cytotoxic injury (ionizing radiation) with or without pretreatment with the differentiating agent DMF have presented a complete set of data for interpretative purposes.

(a) The first important area for discussion concerns the impact of DMF on intrinsic radiosensitivity. It may be seen from Table 1 that both clone A and clone D show a reduction in the $D_0$ parameter, indicating an induced deficit to accumulate sublethal injury. For clone A, there is a 46% decrease in $D_0$, while for clone D, there is a 28% decrease. Therefore, the effect of DMF on these two cell lines is very similar and is similar to effects on exponentially growing cells we have previously reported (10). This sensitization (reduction in $D_0$) in the low dose region of the survival curve is important in that these doses are similar to the typical range of doses per fraction used in conventional radiotherapy regimens and suggest that a greater cell-killing effect would be achieved if DMF were administered prior to or during the time of irradiation.

(b) The actual mechanism of this sensitization is unknown at this time. However, Cordeiro and Savarase (21) have recently shown that treatment of clone A cells with 0.8% DMF will totally deplete the intracellular content of glutathione. This effect is mimicked by treatment with 7.5 mM buthionine sulfoximine and is reversible by the addition of 0.5 mM L-cysteine back to the cultures. It is possible, then, that the reduction in $D_0$ observed with DMF treatment is a reflection of a decreased ability of the cells to accumulate SLDR as a result of glutathione not being available to act as a free radical scavenger.

(c) This sensitization is definitely not due to inhibition of the enzymatic repair of SLD, as Charts 6 to 8 clearly show that DMF had no effect on SLDR in either clone A or clone D.

**Table 2**

<table>
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<tr>
<th>Tumor subpopulation</th>
<th>Correlation coefficient</th>
<th>n</th>
<th>$D_0$ (Gy)</th>
<th>$D_0$ (Gy)</th>
<th>Correlation coefficient</th>
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<td>Clone A split-dose studies at time (h)</td>
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<td>0.98&lt;sup&gt;d&lt;/sup&gt; (42)</td>
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<td>6.10</td>
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<td>1.99</td>
</tr>
</tbody>
</table>

<sup>a</sup> The correlation coefficients of the linear regression fit of the data to define $D_0$ were determined (17).

<sup>b</sup> Mean ± SE.

<sup>c</sup> Statistically significant at the 0.05 level of confidence (17).

<sup>d</sup> Numbers in parentheses, number of data points used to determine the correlation coefficients.
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![Chart](chart.png)

Chart 8. Recovery from sublethal radiation damage in clone A and clone D human colon tumor subpopulations. Cells were given a single dose of X-rays sufficient to reduce survival after immediate replating to about 1%, incubated at 37°C, and then given a second exposure to a total of 8 Gy at various times after the first dose. Points, mean; bars, SE.

(d) In Chart 4, it is clearly shown that DMF treatment increased both the rate and the extent of PLDR in both cell lines, although somewhat greater in clone D (the cell line which exhibited the greater amount of PLDR in the untreated condition). The mechanism by which this effect is expressed is also not understood. Since the percentage of G₂-phase cells is not significantly increased by DMF treatment, it is unlikely that cell cycle redistribution could account for this observation. Inhibition of the synthesis of poly(ADP-ribose) has been shown to be associated with decreased levels of PLDR (22). It is unknown at this time the extent to which DMF modifies levels of poly(ADP-ribose) synthesis in these cells. However, another differentiating agent, sodium butyrate, which produces similar results in terms of increased expression of PLDR after X-irradiation in these two cell lines has been shown to increase synthesis of poly(ADP-ribose) by 2–4-fold (23). This is definitely an area for further investigation.

In summary, therefore, it seems that polar solvents such as DMF act to enhance acute single dose radiation cell killing (Chart 3) and to change the relationship of the cell with its environment to increase the extent of the PLDR process, but they have no discernible effect upon the SLDR process. The impact of these in vivo data on the in vivo use of DMF, either alone or in combination with agents such as X-irradiation, is not yet fully established. We have recently shown that N-methylformamide, when combined with photon irradiation on a different human colon tumor line (DLD-2) xenografted in nude mice, does enhance in vivo radiosensitivity (15). Additional in vivo studies are currently being performed to determine the best utilization and scheduling of polar solvents, X-rays, and other cytotoxic agents in experimental therapeutic protocols.

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