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Detoxification ability and toxicity of quinones in mouse and human tumor cell lines used for anticancer drug screening

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Abstract The in vitro testing of antitumor drugs involves the use of mouse and human tumor cells. In particular, there is interest in developing agents active against human solid tumors. We examined several biochemical parameters that may contribute to the differential sensitivity of the cell lines used in our laboratory to the toxic effects of antitumor compounds. The tumor cell lines examined were of mouse (colon 38, L1210 leukemia, and C1498 leukemia) and human origin (CEM leukemia, CX1 colon, H116 colon, HCT8 colon and H125 lung). Quinone reductase activity was markedly different between leukemia and solid-tumor cell lines of either mouse or human origin, with increased activity being observed in the solid-tumor cell lines relative to the leukemia lines. GSH transferase activity also was generally increased in solid-tumor relative to leukemia cell lines. Superoxide dismutase activity and thiol levels were similar in leukemia and solid-tumor cell lines, except that thiol levels were very low in colon 38. Mouse cell lines from in vitro passage had somewhat higher activity of superoxide dismutase and thiol levels than did cells maintained in vivo, indicating relatively increased antioxidant defenses. The toxicity of 2,3-dimethoxy-1,4-naphthoquinone, a model quinone that exerts its toxic effects via production of reactive oxygen species, was significantly lower in mouse lines maintained in vitro than in those tested in vivo, whereas the toxicity of another quinone, menadione, was just slightly lower. Quinone reductase activity, GSH transferase activity, and thiol levels were significantly higher in the human lines than in the mouse lines. Accordingly, the toxicity of both quinones tended to be lower in the human lines than in the mouse lines.

Key words Quinone toxicity · Leukemia · Solid tumors Detoxification systems

Abbreviations *GSH* Glutathione · *S*-15 15,000-*g* supernatant

Introduction

The development of antitumor drugs has historically relied mainly upon primary testing in lymphocytic leukemias of mice. This has resulted in a paucity of agents that are selectively toxic to solid tumors, and newer drug-discovery efforts have been targeted at human solid tumors [1–4]. In our laboratory, the primary in vitro testing of potential anticancer agents involves use of mouse L1210 leukemia, colon 38, and a human solid tumor (CX1, H116, H125, or HCT8). Agents that are found to be selectively toxic to solid tumor cells in vitro are then tested against solid tumors in vivo.

The toxicity of antitumor compounds in various tumor cell lines may be governed, at least in part, by the ability of the cells to metabolize the compound. Many investigators have examined the role of metabolism in drug toxicity and resistance (reviewed in [5–11]). In the present study, we quantified the activity of select detoxification systems and the toxicity of two model quinones, menadione and 2,3-dimethoxy-1,4-naphthoquinone, in the cell lines used in our drug-discovery efforts. In addition to four human solid tumors, we examined human CEM leukemia and three mouse lines passaged both in vitro and in vivo (L1210, C1498, and colon 38). The origins of these cell lines are given in Table 1.

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Table 1 Origin of the mouse and human tumor cells lines used in the present study

Cell line	Tumor of origin
Mouse cell lines:	
C1498	Leukemia
L1210	Leukemia
Colon 38	Colon
Human cell lines:	
CEM	Leukemia
CX1	Colon
H116	Colon
HCT8	Colon
H125	Lung

The mouse tumor cells utilized for routine anticancer compound screening in our laboratory are maintained by passage through mice to ensure that the tumorigenic properties of the cells are not diminished. The human tumor cell lines, however, are maintained by passage in vitro, mainly due to the lack of a suitable host. To determine whether differences between the human and mouse lines could be affected by the method of passage, mouse lines maintained in vitro were compared with those maintained in vivo.

The detoxification systems we examined were quinone reductase activity, glutathione (GSH) transferase activity, thiol levels, and superoxide dismutase activity. Although there are exceptions, these detoxification mechanisms are generally thought to result in protection from toxicity. Quinone reductase can detoxify many quinone-containing compounds by two-electron reduction, thereby decreasing the extent of one-electron reduction and formation of reactive free radicals [10]. GSH transferase and thiols are involved in the detoxification of a large variety of electrophilic compounds via conjugation [5–8, 11]. For compounds that generate oxygen free radicals during their metabolism, thiol levels and superoxide dismutase activity appear to be an important protective mechanism [6, 9].

The two quinones tested for toxicity in the cell lines, menadione and 2,3-dimethoxy-1,4-naphthoquinone, were chosen on the basis of their known mechanisms of action. Menadione can be detoxified via two-electron reduction by quinone reductase, and inhibition of this enzyme results in increased menadione toxicity [12]. Reduction by one electron to form a free radical is thought to be responsible for the toxic effect of menadione via generation of reactive oxygen species and arylation of cellular nucleophiles [10, 13]. 2,3-Dimethoxy-1,4-naphthoquinone is a derivative of menadione that redox cycles just as rapidly as menadione; however, it does not arylate nucleophiles [13]. The toxicity of both quinones has been shown to be mediated by reactive oxygen species, whereas menadione can also exert its toxic effects via arylation of nucleophiles [10, 12–16].

Materials and methods

Cell culture

The tumor cell lines were obtained from the Division of Cancer Treatment, National Cancer Institute. The mouse tumor cells utilized were maintained by passage either in culture or in mice. For passage of L1210 and colon 38 in mice, 30 to 60-mg fragments were trocared subcutaneously in the mouse strain of origin (C57B1/6 for colon 38 and DBA/2 for L1210). C1498 was maintained in C57B1/6 mice by intravenous passage and cells were recovered from spleens by pushing the spleen through a 100-mesh screen. The tumors were removed after 17–21 days. The tumor cells from three animals were combined and homogenized as described below. Tumor cell lines passaged in vitro were also used, and these were nearly confluent and in the log phase of growth when utilized. Cells that grew attached to tissue-culture plates were removed by scraping.

The L1210 and C1498 leukemia lines were maintained in RPMI 1640 medium supplemented with 10% (by vol.) calf serum. The same medium supplemented with 15% calf serum was used for the colon 38 line. For human CEM leukemia, RPMI 1640 supplemented with 20% calf serum was used. All the other human lines were maintained in Fisher's-CMRL 1066 medium (1:1 v/v), which was supplemented with 11% fetal bovine serum for CX1, H116, and H125 and with 11% horse serum for HCT8. All media were obtained from Gibco (Gaithersburg, Md) and contained 2 m*M* l-glutamine, 100 units penicillin/ml, and 100 μg streptomycin/ml.

Enzyme assays

Cells from continuous culture (log phase cultures that just reached confluence) were washed twice in phosphate-buffered saline (10 m*M* phosphate, pH 7.4, 2.7 m*M* potassium chloride, and 138 m*M* sodium chloride), and they were then suspended in 250 m*M* sucrose, 50 m*M* TRIS (pH 7.4), and 1 m*M* ethylenediamenetetraacetic acid (EDTA). The cells were lysed by being pulled through a 23-gauge needle several times, and disruption of cells was verified microscopically. Tumor cells were also obtained from in vivo passage using small, nonnecrotic tumors. These tumors were homogenized in the above-mentioned sucrose buffer with a polytron. All tumor cell preparations were centrifuged at 15,000 g for 15 min. The supernatant (S-15) was analyzed for various detoxifying systems by spectrophotometric assays using a Hewlett-Packard 8451A diode-array spectrophotometer. The assays have previously been described in more detail [17] and are briefly summarized in the following two paragraphs. Protein levels in the S-15 were quantified by the Biuret method [18].

Quinone reductase activity was quantified from the reduction of succinoylated cytochrome *c* in incubations with menadione, nicotinamide adenine dinucleotide (NADH), and S15. Some incubations also contained 0.1 mg superoxide dismutase/ml to yield quinone reductase as the non-superoxide dismutase-inhibitable rate. GSH transferase activity was quantified from the rate of 1-chloro-2,4-dinitrobenzene conjugation with GSH. Non-protein thiol levels in the S15 were quantified by reaction with Ellman's reagent after precipitation of proteins with perchloric acid using 5% by vol. of 60% perchloric acid. Superoxide dimutase activity was quantified by the ability of S15 to inhibit the rate of xanthine oxidase-catalyzed superoxide production from hypoxanthine, using cytochrome *c* to measure superoxide production; 1 unit of superoxide dismutase activity was defined as the amount of protein required to inhibit superoxide production by 50% and was calculated from curves using varying concentrations of S15.

Cytotoxicity

The cytotoxicity of two model quinones was tested in the cell lines examined. Menadione (2-methyl-1,4-naphthoquinone) was purchased from Sigma Chemical Co. (St. Louis, Mo.). 2,3-Dimethoxy-1,4-naphthoquinone was synthesized by the method of Gant et al. [13] from 2,3-dichloro-1,4-naphthoquinone. The identity of the compound was confirmed by mass spectral analysis (m/e = 218).

Each quinone was dissolved in ethanol and tested for cytotoxicity by the disc-diffusion assay [2]. Briefly, leukemia and solid tumor cells were plated in soft agar in 60-mm petri dishes using an appropriate number of cells to result in about 400 colonies/plate in controls. Known amounts of each compound were placed on a filter disc that was then dried and placed on the previously plated petri dish. After incubation for 6–10 days, the zone of colony inhibition around the disc was measured; 20 zone units of colony inhibition corresponds to a radius of 6.5 mm around the disc.

Statistical analyses

In all, 4 enzymes were assayed 2–6 times/cell line, yielding sample sizes of 30–38 observations/enzyme. Square root transforms of each enzyme activity level were used to normalize the data. Means and standard deviations are reported in the original measurement scale to facilitate interpretation of the results. Mean (square root of) enzyme activity was compared across the 11 cell lines using 1-way, unbalanced, univariate analysis of variance (ANOVA). The variable number of repetitions performed for each assay resulted in missing data patterns that precluded an effective multivariate ANOVA of the four enzymes simultaneously.

The toxicity induced by 2 quinones (each used at 3 doses) was recorded for each of the 11 cell lines. Toxicity observations were available for 66 combinations ($2 \times 3 \times 11$) of drug, dose, and cell line. The toxicity levels (zones of inhibition) also required square root transformation to satisfy better the normality assumptions of ANOVA, but they are again reported in their original scale for descriptive statistics. The combined effects of drug, dose, and cell line upon the mean (square root of) toxicity level were explored using three-way, unbalanced, univariate ANOVA. Interaction effects (e.g., drug $\times$ cell line) were tested to determine whether stratified analyses of subgroups were necessary.

For both the enzyme-activity data and the toxicity data, when significant differences across the 11 cell lines were detected in an ANOVA, various pairs of cell lines were then compared using the Tukey-Kramer multiple-comparisons procedure. Paired comparisons were reported as significant if $P < 0.05$ in the multiple-comparisons sense. For comparisons of sets of cell lines (e.g., solid tumor versus leukemia; mouse versus human), linear contrast vectors were employed in the ANOVA. Statistical analyses were performed via the SAS 6.08 software, especially using the General Linear Models (GLM) procedure [19].

Results

Quinone reductase.

The activity of quinone reductase was significantly higher in solid-tumor cell lines relative to leukemias ($P < 0.05$), and this was observed in both mouse and human cell lines. Although there were significant differences between the mouse tumor cells passaged in vivo and those maintained in vitro, the activity of quinone reductase was significantly higher in colon 38 than in C1498 or L1210 leukemia in either case (Fig. 1).

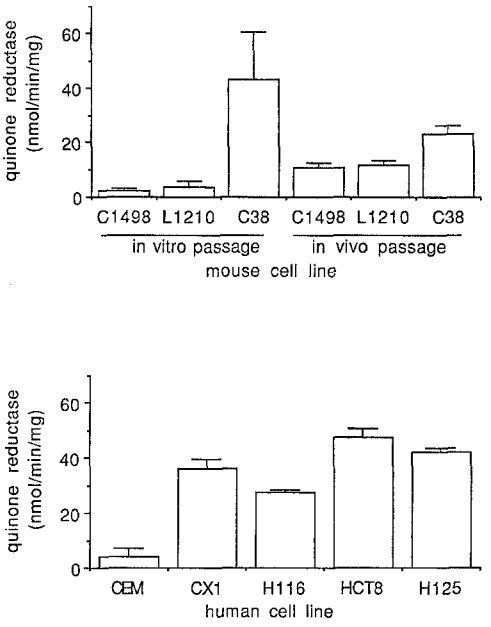

Fig. 1 Mean activity of quinone reductase detected in the S-15 of mouse and human tumor cell lines. *Error bars* depict the standard deviation

In the human cell lines, quinone reductase activity was also significantly higher in the solid-tumor cell lines than in CEM leukemia. All the human solid-tumor cell lines had significantly greater quinone reductase activity than did mouse C1498 from either in vivo or in vitro passage. Nearly the same was true for L1210, except that the quinone reductase activity of human H116 was not significantly higher than that of mouse L1210 in vivo. In addition, human HCT8 had significantly greater activity than did mouse colon 38 from in vivo passage.

GSH transferase

GSH transferase activity was significantly higher in colon 38 tumor cells passaged in vivo than in L1210 or C1498 from either passage technique. The three mouse lines from in vivo passage (as a group) had significantly greater activity than those passaged in vitro (Fig. 2).

In the human cell lines, significantly higher activity of GSH transferase was observed in HCT8 colon tumor-cell lines relative to CEM leukemia, but the activity seen in the other three human solid-tumor cell lines (CX1, H116, and H125) was not significantly higher than that detected in CEM leukemia (Fig. 2). Human colon HCT8 had significantly higher activity of GSH transferase than did all six mouse tumors except colon 38 in vivo. Human CX1 and H125 had significantly higher activity as compared with L1210 and C1498 (regardless of passage type) but did not do so in comparison with colon 38.

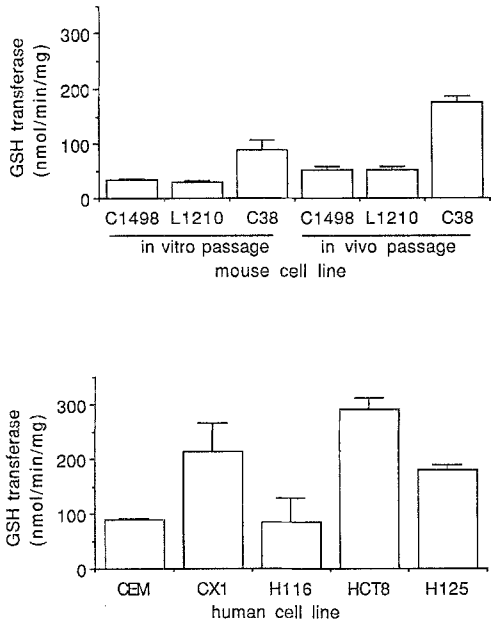

Fig. 2 Mean activity of GSH transferase detected in the S-15 of mouse and human tumor cell lines. *Error bars* depict the standard deviation

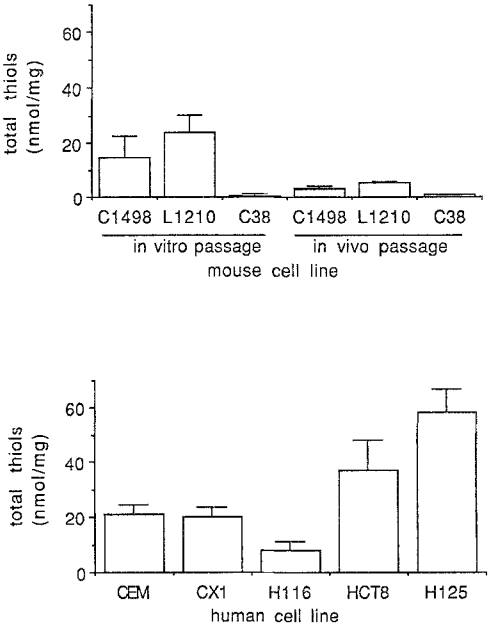

Fig. 3 Mean levels of total thiols detected in the S-15 of mouse and human tumor cell lines. *Error bars* depict the standard deviation

Thiol levels

The levels of total thiols were significantly lower in colon 38 cells than in either L1210 or C1498 leukemia, whether from in vitro or in vivo passage (Fig. 3). Higher levels of thiols were observed in mouse leukemia lines from in vitro passage relative to those passaged in vivo, but not significantly so. The levels of thiols were similar in colon 38 maintained by either passage technique.

In the human tumor cell lines, the only solid tumors that exhibited significantly higher levels of thiols relative to CEM leukemia was H125. Comparisons between human and mouse lines were also made. Human H125 had significantly higher thiol levels than did all mouse lines. CEM and CX1 lines had significantly higher levels than did C1498 from in vivo passage alone or colon 38, regardless of passage type. Human H116, HCT8, and H125 showed significantly higher thiol levels than did all mouse lines except L1210 from in vitro passage.

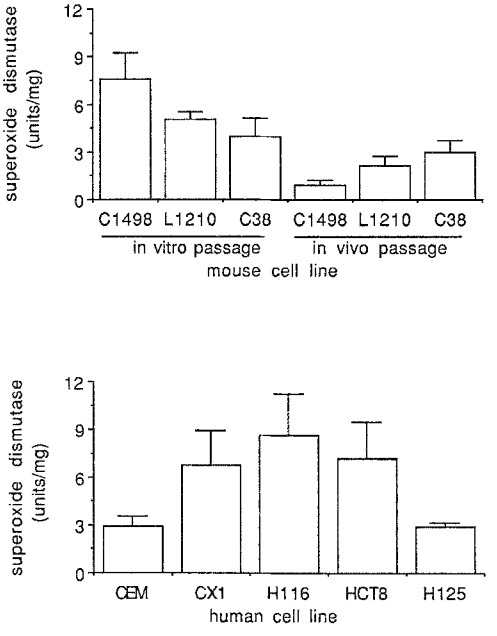

Fig. 4 Mean activity of superoxide dismutase detected in the S-15 of tumor cell lines. *Error bars* depict the standard deviation

Superoxide dismutase

In mouse lines maintained in vitro, there was lower activity of superoxide dismutase in C1498 and L1210 mouse lines relative to colon 38. For the cell lines passaged in vivo, activity in colon 38 was higher than that in C1498 or L1210, but not significantly so (Fig. 4). Higher superoxide dismutase activity in each of the three mouse cell lines was observed in the in vitro-maintained cells versus those maintained in vivo, but only the difference found for C1498 leukemia was significant.

Among human tumor lines, H116 cells exhibited significantly higher superoxide dismutase activity than did CEM or H125 cells (Fig. 4). In the comparison of human and mouse lines, human H116 had significantly higher activity than did all in vivo mouse tumor cells. Mouse C1498 maintained in vitro had significantly higher activity than did human CEM or H125. Mouse

C1498 and L1210 cell lines from in vivo passage had significantly lower superoxide dismutase activity than did human CX1, H116, or HCT8 cell lines.

Cytotoxicity

With the exception of CEM, menadione was generally more toxic in the mouse lines than in the human lines (Fig. 5). A suggestive interaction effect ($P = 0.055$) between cell line and drug upon toxicity levels indicated that a drug-stratified analysis was appropriate. There was no significant interaction effect between cell line and dose (for either drug) hence, the cell-line main effect can be reported averaged over the (strong) main effect of dose. Menadione was significantly more toxic to primary C1498 than to the four human solid tumors CX1, H116, HCT8, and H125. After adjustment for dose effect, menadione was significantly more toxic to CEM leukemia than to all the other human lines except CX1 as determined from Tukey multiple comparisons performed in follow-up to the 2-way ANOVA of the menadione-toxicity data across all 11 cell lines, and all 3 doses.

There was no significant difference in 2,3-dimethoxy-1,4-naphthoquinone toxicity across the 11 cell lines tested (Fig. 6). In an analysis of the toxicity data in the six mouse lines only, the toxicity of 2,3-dimethoxy-1,4-naphthoquinone was significantly increased in the three lines cultured in vivo (as a group) versus the three cell lines from in vitro passage. There was a similar trend for menadione toxicity in the six mouse lines, but this was not significant.

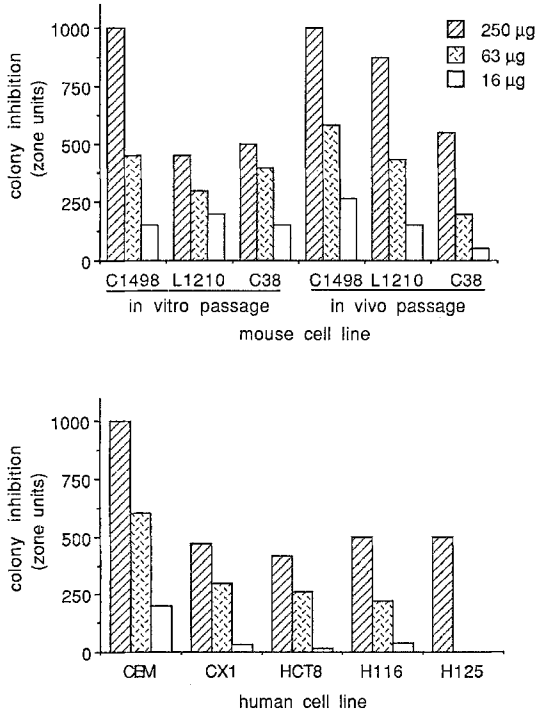

Fig. 5 Cytotoxicity of menadione in tumor cell lines as determined by the disc-diffusion assay. Cytotoxicity is expressed as the zone of colony inhibition around a paper disc impregnated with menadione (20 zone units = 6.5 mm). Three different amounts of menadione were used on the disc as indicated

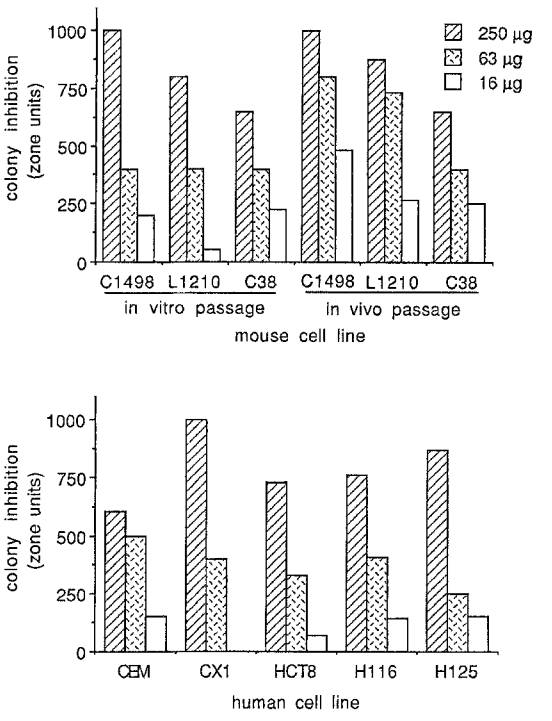

Fig. 6 Cytotoxicity of 2,3-dimethoxy-1,4-naphthoquinone in tumor cell lines as determined by the disc-diffusion assay. Cytotoxicity is expressed as the zone of colony inhibition around a paper disc impregnated with 2,3-dimethoxy-1,4-naphthoquinone (20 zone units = 6.5 mm). Three different amounts of 2,3-dimethoxy-1,4-naphthoquinone were used on the disc as indicated

Overall, 2,3-dimethoxy-1,4-naphthoquinone was more toxic than menadione. Due to the interaction effect (noted above) of drug and cell line upon toxicity levels, drug effects could be assessed only in a stratified analysis (e.g., within subgroups). We chose to stratify cell lines by species of origin. Among the 6 mouse cell lines combined, 2,3-dimethoxy-1,4-naphthoquinone was significantly more toxic ($P = 0.034$) than menadione, even after adjustment for the very strong effect of dose ($P < 0.0001$) in a two-way ANOVA. Among the 5 human cell lines combined, 2,3-dimethoxy-1,4-naphthoquinone was found to be marginally significantly more toxic ($P = 0.052$) than menadione after adjustment for the very strong effect of dose ($P < 0.0001$) in a two-way ANOVA.

Discussion

In this study, quinone toxicity and the activity of select detoxification pathways were examined in 11 tumor cell lines. In particular, we were interested in whether any differences might exist between the various types of

cells examined: solid-tumor versus leukemia cell lines, cell lines passaged in vitro versus those passaged in vivo, and human versus mouse lines.

In the comparison between the solid-tumor and leukemia cells examined in this work, thiol levels and superoxide dismutase activity were similar (except in colon 38 cells, which had low levels of thiols), whereas solid tumors tended to have higher activity of GSH transferase and quinone reductase than did leukemia lines. The only exception was human H116, which had GSH transferase activity that was similar to that of CEM leukemia. This indicates that drugs that are activated, rather than detoxified, by quinone reductase would be relatively more effective in solid tumors than in leukemia. Examples of drugs that are bioactivated by quinone reductase include mitomycin C [20] and aziridinylbenzoquinones [21]. In contrast, other quinone-containing compounds can be detoxified rather than activated by quinone reductase [22]. Protection from menadione toxicity is known to be mediated by two-electron reduction via the quinone reductase DT diaphorase, which competes with one-electron reduction of the compound and the subsequent production of toxic reactive oxygen species [10, 12, 19, 23]. Menadione toxicity did tend to be higher in the leukemia lines than in the solid tumor lines, the latter of which had relatively higher quinone reductase activity. The toxicity of menadione was similarly quite high in CEM leukemia, which had lower quinone reductase activity than did all the other human lines.

For the mouse leukemia lines, the in vivo-passaged cells had lower activity of superoxide dismutase and thiol levels than did lines passaged in vitro whereas GSH transferase and quinone reductase activities were similar. Superoxide dismutase and glutathione have been suggested to function as an efficient chain-breaking antioxidant system [9]. The relatively higher antioxidant capacity of in vitro-passage lines may be a function of the oxygen concentration of culture conditions requiring increased antioxidant defenses or it could be due to the cell-cycle phase of the tumor. It has previously been shown that log-phase in vitro cultures of tumor cells have higher levels of GSH than do tumor cells from the animal whereas plateau-phase in vitro cultures have GSH levels that are more similar to those of cells grown in vivo [24]. The increased antioxidant capacity of the in vitro-cultured cells used in this work appeared to influence the toxicity of 2,3-dimethoxy-1,4-naphthoquinone more strongly than that of menadione. In the comparison of toxicity data from the six mouse lines, the toxicity of 2,3-dimethoxy-1,4-naphthoquinone was significantly increased in the cells cultured in vivo versus those from in vitro passage. There was a similar trend for menadione toxicity, but this was not significant, possibly because menadione toxicity can be mediated both by redox cycling and by nucleophile arylation [13]. The toxicity of both menadione and 2,3-dimethoxy-1,4-naphthoquinone was also significantly higher in primary cultures of C1498 than in several other cell lines. This may be related to the observation that primary C1498 had significantly lower levels of superoxide dismutase than did any other cell line as well as fairly low levels of thiols.

Possible differences between human and mouse cells were also examined. Thiol levels and enzyme activities examined in this work were generally the same order of magnitude in mouse and human cell lines (Figs. 1–4). In agreement with these results, mouse colon 38 has previously been shown to have levels of GSH and GSH transferase activity similar to those observed in human colon-tumor biopsy tissues [25]. In our work, the levels of thiols, quinone reductase, and GSH transferase activity were significantly greater in human lines than in the mouse lines, and this did not appear to be due to differences in the method of passage. The toxicity-test results (Figs. 5, 6) are in general agreement with that observation in that the toxicity of both quinones examined did tend to be higher in the mouse cell lines than in the human lines.

In summary, the present data suggest that the detoxification systems examined influenced quinone toxicity. In particular, there were greater differences between the leukemia and solid-tumor lines than between the mouse and human tumors. This supports the observation that primary anticancer drug screening with leukemia lines may be inadequate for the discovery of agents active against solid tumors [1–4].

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