ABSTRACT

In contrast to most metastatic cancers, testicular germ cell tumors are cured in more than 80% of patients using cisplatin-based combination chemotherapy. Testis tumor cells in vitro retain their sensitivity to chemotherapy drugs, radiation, and other stresses, such as heat shock. Having shown that this is associated with low constitutive levels of heat shock protein (HSP) 27, we determined the effect of overexpression of HSP27 on the heat and drug sensitivities of a human testis tumor cell line, 833K. Cells were cotransfected with plasmids containing a neomycin resistance gene and the full-length human HSP27 gene, and four clones that overexpressed HSP27 by factors of 3.7-38.3-fold compared with the parental cells were selected. The overexpressing cells were more resistant to heat shock, cisplatin, and doxorubicin, and this was associated with modest increases (17-30%) in population doubling times and a small reduction in the number of S-phase cells. These results suggest that the low constitutive levels of HSP27 in testis tumor cells may contribute to the sensitivity of testicular germ cell tumors to chemotherapy, and that targeting HSP27 may improve response rates in other types of cancer.

INTRODUCTION

Expression of the small HSP27 is associated with the response of cancer cells to chemotherapeutic drugs and heat shock. For example, transfection of the human gene for HSP27 into Chinese hamster ovary cells resulted in resistance to doxorubicin, colchicine, and vincristine but not 5-fluorouracil or nitrosoureas (1). Similarly, induction of HSP27 expression following stress can result in resistance to doxorubicin and actinomycin D (2-5) and heat shock (6-9). These interactions can be reciprocal, because another chemotherapeutic drug, cisplatin, can induce HSP27 and thermotolerance in Ehrlich ascites tumor cells (10, 11).

Recent studies indicate that phosphorylation plays a key role in the regulation of HSP27 function and its contribution to survival following stress (12, 13). It is proposed that phosphorylation induces conformational changes in HSP27, resulting in a lower binding efficiency of HSP27 for the barbed ends of microfilaments and consequent stabilization of the cytoskeleton (13). It is the maintenance of actin filament integrity that is believed to enhance survival following exposure to stress. For example, Chinese hamster cells transfected with the gene for wild-type HSP27 had an increase in the stability of their microfilaments and were thermotolerant and resistant to cytochalasin D. In contrast, cells transfected with a mutant nonphosphorylatable form of HSP27 showed little thermotolerance and were similar to control cells in their sensitivity to cytochalasin D (13).

There is also a correlation between the lack of expression of HSP27 and drug sensitivity. Cure rates for metastatic testicular germ cell tumors exceed 80%, whereas, in stark contrast, most other advanced cancers are incurable. This differential sensitivity of testis tumor cells to chemotherapeutic drugs such as cisplatin is maintained in vitro (14-17). Testis tumor cells are also more sensitive to heat shock and express low levels of HSP27 (18). Therefore, the inherent sensitivity of testis tumor cells to heat and cisplatin may be associated with their low constitutive expression of HSP27 (18). To test this hypothesis, we transfected the human testis tumor cell line 833K with the full-length human HSP27 gene (19) and analyzed the effect of overexpression of the protein on heat and drug sensitivity and the growth characteristics of the cells.

MATERIALS AND METHODS

Cells and Culture Conditions. The human testis cancer cell line 833K (20) and clones of transfected 833K cells were grown under identical conditions as monolayers in tissue culture flasks (Life Technologies, Inc., Paisley, United Kingdom) in RPMI 1640 medium (Life Technologies), supplemented with 10% (v/v) heat-inactivated FCS (Imperial Laboratories, Andover, United Kingdom) and 2 mM l-glutamine (Life Technologies), at 36.5°C in a humidified atmosphere of 5% CO2 in air.

Plasmids. The plasmid pSV2711 was obtained by cloning the full-length human HSP27 gene (19) into the mammalian expression vector pBluescript (Invitrogen, San Diego, CA). The gene is under control of an SV40 promoter, allowing for constitutive expression of HSP27. The plasmid pSV2neo contains a neo resistance gene and was used for cotransfection.

Transfection. The human testis cell line 833K was cotransfected with pSV2711 and pSV2neo using a calcium phosphate technique. Briefly, 2.5 × 106 exponentially growing cells were seeded into T25 tissue culture flasks and incubated at 36.5°C for 22 h. Following a medium change and incubation for 4 h, 5 ml fresh medium and then 1 ml DNA solution were added. The DNA solution was prepared by adding 500 µl 2X HBS (280 mM NaCl, 10 mM KCl, 15 mM Na2HPO4, 2H2O, 12 mM dextrose, and 50 mM HEPES) dropwise, with mixing to 500 µl of 0.28 M CaCl2 solution containing the plasmid(s). Routinely, 2.5 µg pSV2neo and 40 µg pSV2711 were added to each flask. After a 6-h incubation, the cells were washed twice in medium and then incubated in fresh medium for 36 h at 36.5°C before adding 150 µg/ml G418, a concentration that kills all parental 833K cells. After 2-3 weeks of selection, resistant clones were isolated and expanded, and frozen stocks were made. For all experiments, parental 833K cells and all clones were used over a maximum of 12 passages to minimize changes that might occur as a result of long-term culture.

Immunoblot Analysis. HSP27-overexpressing clones were identified by Western blotting of protein obtained from G418-resistant clones. Cell lysates were prepared as described previously (18) by resuspending trypsinized and PBS-washed cells in a lysis buffer consisting of 40 mM Tris (pH 6.8), 2% SDS, 10% glycerol, 5% ß-mercaptoethanol, and 0.002% bromophenol blue, followed by boiling for 3 min. A volume of lysate corresponding to 50,000 cells (about 23 µg protein) or a known dilution was run on a 12.5% SDS polyacrylamide gel, and proteins were transferred to nylon Hybond membranes (Amersham International, Amersham, United Kingdom). The membranes were incubated for 90 min at room temperature with monoclonal antibodies specific for HSP27 (1.0 µg/ml in PBS/BSA; provided by Dr. Roger King, University of Surrey, Surrey, United Kingdom), anti-HSP73/72 (0.2 µg/ml in PBS/BSA; Stressgen SPA-820), or anti-HSP90 (0.2 µg/ml in PBS/BSA; Stressgen SPA-840), followed by horseradish PO-labeled, rabbit antimoise or antirat antibodies (diluted 1:35,000 in PBS/BSA; DAKO, High Wycombe, United Kingdom). The proteins were visualized using enhanced chemiluminescence (Amersham), and the M, of proteins were estimated by reference to standards (Bio-Rad broad range). Membranes to be reprobed with a different primary antibody were treated with 2% SDS-PAGE sample buffer, heated at 90°C for 10 min, and run on a 12.5% SDS polyacrylamide gel.
antibody were incubated in stripping buffer [62.5 mM Tris (pH 6.8), 2% SDS, and 5% β-mercaptoethanol] for 30 min at 50°C, washed three times in PBS for 5 min, and then processed for immunoblotting as described above. Relative amounts of HSP present in samples processed on the same membrane were quantified using scanning densitometry using an Imaging Densitometer (Bio-Rad GS-670; Hemel Hempstead, United Kingdom). Routinely, HSP levels in 833K cells transfected with both pSV2711 and pSV2neo were compared with those in pSV2neo (neo only)-transfected and parental 833K cells. For preliminary experiments, Western blotting was performed twice for each sample. For clones chosen for additional investigations (clones 1-4 in “Results”), the fold increase in HSP27 levels was determined by blotted two to three independently prepared lysates of each clone on three separate occasions. Dilutions of lysates were also blotted to ensure that the linearity of the film was not exceeded when overexpressing clones were compared with controls. For all blots, accurate loading of samples was monitored by staining polyacrylamide gels with Coomassie blue and Western blotting membranes with Ponceau red (Sigma Chemical Co., Poole, United Kingdom). In addition, to eliminate possible clonal variability, four neo-only transfected clones were combined to make a neo pool. Individual clones were grown separately and pooled prior to use in experiments.

**Colony-forming Assays.** The heat and drug sensitivities were compared using a colony-forming assay, as described previously (18). Cells were seeded into 5-cm Petri dishes at densities to produce approximately 200 colonies per dish in the controls and were incubated for 22 h at 36.5°C. Heat sensitivity was measured by incubating cells at 45 ± 0.2°C for periods of up to 100 min and then returning cells to 36.5°C and incubating for 12–14 days. Controls were maintained at 36.5°C.

Cisplatin and doxorubicin (Sigma) were prepared as 1-mg/ml stocks in distilled, deionized H2O, warmed to 37°C, and added repeatedly on a Whirlimixer (Fisons, Loughborough, United Kingdom), and added to cells immediately after preparation. Sensitivities were estimated following continuous exposure to a range of drug concentrations, using colony-forming assays as described above.

Colonies were fixed (70% ethanol) and stained (10% Giemsa in H2O). The number of colonies consisting of 50 or more cells was determined, and the percentage colony-forming efficiency of heat- and drug-treated cells was calculated as proportions of the colony-forming efficiency in the appropriate control groups. For each assay, two to three Petri dishes were prepared for each treatment, and assays were repeated at least three times. For each assay, IC50 values for controls and HSP27-overexpressing clones were determined using an INSTAT program (GraphPad Software).

**Intracellular Platinum Accumulation.** Between 2.5 and 4 × 106 cells were seeded into 5-cm Petri dishes, incubated at 36.5°C for 22 h, and exposed to 50 μM cisplatin for 1 h. Following three washes in ice-cold PBS, the cells were scraped off the dishes, suspended in 0.5 ml PBS, and stored at -20°C. After sonication (Soniprep 150 MSE), the total cellular content of cisplatin was determined by atomic absorption spectroscopy (Perkin Elmer). A 50-μl aliquot was used to estimate the protein concentration of the sonicates (bicinchoninic acid; Pierce, Rockford, IL), and cellular platinum levels were expressed as nmol platinum/mg protein.

**MTT Assays: Estimation of Cell-doubling Time.** For HSP27-overexpressing clones and controls, 300 μl medium containing 1500 cells were added to each of eight wells (one row of five 96-well, flat-bottom tissue culture plates (Life Technologies) and incubated for 1, 2, 3, 4, or 5 days at 36.5°C. At each time point, one plate was taken, and 50 μl of a freshly prepared solution of 5 mg/ml MTT (Sigma) in PBS were added to each well, and the cells were incubated for 3 h at 36.5°C. This mixture was then discarded, and 100 μl DMSO (Sigma) were added to each well and mixed by placing plates on a shaking platform for 15 min. The amount of MTT product in each well was then determined by reading the plates on a Tittertek Multiscan MCC340 plate-reading spectrophotometer at 540 nm. For each assay, a graph of A versus time was constructed, and the doubling time was calculated. Parental 833K and transfected cells were processed simultaneously, and assays were repeated three times.

**FACS Analysis.** Subconfluent monolayers of cells grown in T25 flasks were trypsinized and resuspended in 10 ml medium. Aliquots of 5 × 106 cells in 5 ml medium were then spun down (1000 rpm, 5 min, 4°C), and the cell pellet was resuspended in 1 ml ice-cold PBS. Cells were fixed by slowly adding 3 ml ice-cold 95% ethanol with constant vortexing. Following incubation on ice for 10 min, cells were stored at 4°C overnight. The fixed cells were collected by centrifugation, washed twice in 5 ml PBS, resuspended in 500 μl freshly prepared propidium iodide solution (50 μg/ml propidium iodide, 0.1% sodium citrate, 7.5 μg/ml RNase, and 0.002% NP40; all from Sigma), and incubated for 1 h at room temperature in the dark. FACS analysis was carried out on a Becton Dickinson FACScan.

**RESULTS**

**Transfection of 833K Cells and Identification of HSP27-overexpressing Clones.** Western blotting (Fig. 1) indicated that the levels of constitutively expressed HSP27 in neo-only transfected clones (Lanes 1–4) and a neo pool (Lane 5) were similar to that in parental 833K cells. Thus, the transfection procedure itself did not increase the level of this HSP.

Forty G418-resistant clones were analyzed. Compared with the parental 833K cells, three clones had 3–10-fold, seven clones had 10–20-fold, and three clones contained more than 20-fold higher HSP27 levels. Four clones with increased HSP27 levels ranging from 3.7- to 38.3-fold (mean values derived from three independent determinations) were selected for additional study (Table 1 and Fig. 2). In these clones, there was no increase in the levels of either HSP73/72 or HSP90 compared with the parental 833K cells (Fig. 2).

**Heat Sensitivities.** The heat sensitivities are shown in Table 1 and Fig. 3. Comparing their IC50 values, the control cells (parental 833K, neo-only transfected clone, and neo pool) were not significantly different. However, the three clones with the highest levels of HSP27 overexpression were significantly more resistant to heat compared with parental 833K cells (P < 0.05; Table 1 and Fig. 3).

**Drug Sensitivities.** The sensitivities of the cells to cisplatin and doxorubicin are shown in Table 1 and Fig. 4, a and b. The control cells (parental 833K, neo-only transfected clone, and neo pool) and clone 1 (3.7-fold overexpression of HSP27) were not significantly different from parental 833K cells in their sensitivity to cisplatin. However, compared with the parental 833K cells, clones 2, 3, and 4 were, respectively, 3.8-, 3.7-, and 3.5-fold more resistant.

Similarly, there was no significant difference in the sensitivities to doxorubicin of the control cells (Table 1 and Fig. 4b). However, all four overexpressing clones were significantly more resistant than the parental 833K cells (Table 1), exhibiting increases of 1.6-, 2.5-, 1.3- and 2.6-fold, respectively (Fig. 4b).

**Intracellular Platinum Accumulation.** To determine the influence of HSP27 overexpression on the intracellular accumulation of cisplatin, uptake was compared between the cell lines (Table 2). Similar amounts of cisplatin were taken up by the control cells

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**Fig. 1.** Western blots showing constitutive levels of HSP27 in parental 833K cells and four neo-only transfected clones (Lanes 1–4) obtained from four independent transfection experiments and a neo pool (Lane 5) consisting of four independent neo-only transfected clones also obtained from four independent transfection experiments. For each sample, a volume of cell lysate corresponding to 50,000 cells was separated by SDS-PAGE using a 12.5% resolving gel. HSP27 was detected using a monoclonal antibody and a PO-labeled secondary antibody.
**Table 1** Heat and drug sensitivities and levels of HSP27 expression relative to parental 833K cells

<table>
<thead>
<tr>
<th>Cells/clones</th>
<th>Heat IC50 (mean ± SD) (n)</th>
<th>Cisplatin IC50 (mean ± SD) (n)</th>
<th>Doxorubicin IC50 (mean ± SD) (n)</th>
<th>Relative levels of HSP27</th>
</tr>
</thead>
<tbody>
<tr>
<td>833K</td>
<td>28.3 ± 3.4 (n = 4)</td>
<td>12.2 ± 6.1 (n = 3)</td>
<td>1.1 ± 0.2 (n = 5)</td>
<td>1.0</td>
</tr>
<tr>
<td>neo</td>
<td>27.9 ± 4.3 (n = 5)</td>
<td>17.56 ± 5.5 (n = 4)</td>
<td>1.2 ± 0.5 (n = 4)</td>
<td></td>
</tr>
<tr>
<td>neo pool</td>
<td>29.3 ± 0.7 (n = 2)</td>
<td>18.54 ± 2.1 (n = 2)</td>
<td>1.2 ± 0.1 (n = 2)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>30.5 ± 1.3 (n = 3)</td>
<td>21.1 ± 5.9 (n = 3)</td>
<td>1.7 ± 0.1* (n = 3)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>34.9 ± 3.9* (n = 3)</td>
<td>46.5 ± 7.6* (n = 3)</td>
<td>2.6 ± 0.7* (n = 3)</td>
<td>3.7 ± 0.6</td>
</tr>
<tr>
<td>3</td>
<td>37.5 ± 3.8* (n = 4)</td>
<td>44.9 ± 12.9* (n = 3)</td>
<td>1.4 ± 0.3* (n = 6)</td>
<td>8.3 ± 1.8</td>
</tr>
<tr>
<td>4</td>
<td>39.2 ± 3.1* (n = 4)</td>
<td>43.6 ± 13.6* (n = 3)</td>
<td>2.7 ± 0.4* (n = 3)</td>
<td>22.2 ± 4.1</td>
</tr>
</tbody>
</table>

*IC50 values were calculated using an INSTAT program. n, number of independent experiments.

DISCUSSION

Testis tumor cells are extremely sensitive to cisplatin-based chemotherapy, both in the clinic and in vitro (15, 17). Sensitivity is thus an inherent property of the testis tumor cells, but the biochemical mechanisms involved are unknown. Testis tumor cells are also very sensitive to heat shock, and this is associated with low constitutive levels of HSP27 (18). Here, we demonstrate that overexpression of HSP27 can increase the resistance of testis tumor cells to heat and chemotherapeutic drugs. These results indicate that the sensitivity of testis tumors to such stresses can, at least in part, be accounted for by their low levels of constitutive expression of HSP27.

Comparisons were made between HSP27-overexpressing clones and the parental 833K cells. In addition, comparisons were made with a representative neo-only transfected clone and a pool of four neo-only transfected clones, the latter being included to control for clonal variation. Neither the transfection procedure itself nor subsequent selection of clones in G418-containing medium altered either the levels of constitutively expressed HSP27 or the sensitivities of the control cells to heat and drugs. In the HSP27-overexpressing clones, there was no concomitant increase in either HSP90 or HSP73/72 levels. These findings indicate that the processes of transfection, selection in G418, and overexpression of HSP27 did not induce a...
generalized stress response. Thus, the differences between HSP27-overexpressing clones and parental 833K cells can be attributed to the effects of this HSP alone.

Increased constitutive levels of HSP27 conferred protection against the cytotoxic effects of a heat stress. This finding is in agreement with previous studies showing increased resistance to heat shock following overexpression of HSP27 in Chinese hamster and mouse cells (7), Chinese hamster CCL39 cells (13), and mouse NIH/3T3 cells transfected with human HSP27 (21); and Ehrlich ascites tumor cells (22) and mouse NIH/3T3 cells (23) transfected with mouse HSP25. The mechanism by which overexpression of HSP27 and HSP25 confers increased resistance to heat shock is unknown. However, because heat-induced damage and denaturation of proteins is a major contributor to cytotoxicity (24), the ability of HSP27 to act as a molecular chaperone, protecting proteins from damage and promoting the functional refolding of damaged proteins (25), is likely to account for at least part of its protective role.

The HSP27-overexpressing clones were more resistant to cisplatin than the parental 833K cells, although there was no correlation between the level of HSP27 present in the cells and their resistance to this drug. Previous studies linking heat shock protein expression to cisplatin sensitivity are sparse. It was shown (4) that two breast cancer cell lines with high and low endogenous expression of HSP27 exhibited IC50 values for cisplatin of 77 and 68 μM, respectively. Thus, the cell line with higher levels of HSP27 was slightly more resistant. Cisplatin induced expression of HSP25 in Ehrlich ascites tumor cells, resulting in thermotolerance (10). Conversely, a number of studies have demonstrated that thermotolerant cells, in which levels of HSP27 and other HSPs are raised, do not exhibit an increase in resistance to cisplatin in vitro (26–29) or in vivo (30). Chinese hamster cells overexpressing the human HSP27 gene exhibited a multidrug-resistant phenotype that is not P-glycoprotein mediated (1, 9). However, the effect on cisplatin sensitivity was not investigated. Our study seems to be the first report showing that HSP27 overexpression can confer resistance to cisplatin, although this may be specific to testis tumor cells.

The HSP27-overexpressing clones were also more resistant to doxorubicin, although, as for cisplatin, there was no correlation between the amount of HSP27 expressed in the cells and the degree of resistance attained. Previous studies have also shown that HSP overexpression can result in resistance to doxorubicin. For example, when HSPs were induced prior to drug treatment by elevated temperature or by exposure to arsenite, cadmium, or ethanol, the cells were more resistant to doxorubicin (2, 3, 31). More direct evidence for the involvement of HSP27 in cellular resistance to doxorubicin comes from gene transfection studies. For example, overexpression of human HSP27 in Chinese hamster cells increased resistance to doxorubicin, colchicine, and vinristine but not 5-fluorouracil or the nitrosoureas (1, 9). Similarly, when human breast cancer cells (MDA-MB-231, with low endogenous levels of HSP27) were transfected with the

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**Table 2. Cisplatin uptake and growth characteristics**

<table>
<thead>
<tr>
<th>Cells/clones</th>
<th>Cisplatin uptake (nmol/mg protein)</th>
<th>Population-doubling time (h)</th>
<th>G1 (%)</th>
<th>S (%)</th>
<th>G2-M (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>833K</td>
<td>0.64 ± 0.02 (n = 4)*</td>
<td>24.5 ± 1.9 (n = 3)</td>
<td>34.3</td>
<td>46.7</td>
<td>19.0</td>
</tr>
<tr>
<td>neo</td>
<td>0.67 ± 0.09 (n = 4)</td>
<td>24.1 ± 4.2 (n = 3)</td>
<td>29.8</td>
<td>51.5</td>
<td>18.7</td>
</tr>
<tr>
<td>neo pool</td>
<td>0.64 ± 0.04 (n = 4)</td>
<td>22.6 ± 1.8 (n = 3)</td>
<td>31.5</td>
<td>49.8</td>
<td>18.7</td>
</tr>
<tr>
<td>Clone 1</td>
<td>0.69 ± 0.07 (n = 4)</td>
<td>30.1 ± 2.3 (n = 3)</td>
<td>35.6 ± 7.3*</td>
<td>46.5 ± 0.4</td>
<td>18.0 ± 7.6</td>
</tr>
<tr>
<td>Clone 2</td>
<td>0.69 ± 0.08 (n = 4)</td>
<td>28.8 ± 2.0 (n = 3)</td>
<td>42.3 ± 1.6</td>
<td>39.9 ± 1.7</td>
<td>17.8 ± 3.3</td>
</tr>
<tr>
<td>Clone 3</td>
<td>0.70 ± 0.09 (n = 3)</td>
<td>31.9 ± 0.2 (n = 3)</td>
<td>36.6 ± 1.8</td>
<td>44.2 ± 2.7</td>
<td>19.3 ± 0.9</td>
</tr>
<tr>
<td>Clone 4</td>
<td>0.86 ± 0.07 (n = 3)</td>
<td>31.2 ± 2.6 (n = 3)</td>
<td>36.1 ± 3.0</td>
<td>44.8 ± 3.0</td>
<td>19.0 ± 0.0</td>
</tr>
</tbody>
</table>

* n, number of independent experiments.

* Significantly different from parental 833K cells; P < 0.05.

* Values obtained from two independent cell preparations.
human HSP27 gene, a 6–8-fold overexpression of the protein resulted in a 3-fold increase in resistance to doxorubicin. Conversely, a 3–4-fold down-regulation of HSP27 in the breast cancer cell line MCF-7/MG (with high endogenous levels of HSP27), using HSP27 in the antisense orientation, increased the sensitivity of the cells to doxorubicin (5). The mechanisms whereby raised HSP27 levels increase cellular resistance to doxorubicin remain unknown.

We also investigated whether overexpression of HSP27 modifies certain other characteristics of 833K cells. HSP27 is known to interact with the cytoskeleton (21), and constitutive overexpression in Chinese hamster cells caused an increase in filamentous actin and elevated pinocytotic activity (32). Consequently, HSP27 overexpression might influence cisplatin uptake. However, cisplatin uptake in the overexpressing clones was either similar to or greater than that in the control cells, indicating that the increase in resistance of these cells to cisplatin is not associated with reduced uptake of the drug.

Increased constitutive levels of HSP27 are associated with reduced growth rates in Ehrlich ascites tumor cells (22), human B lymphocytes (33), osteoblasts, and promyelocytic leukemia cells (34). These studies, together with the finding that HSP27 interacts with the cytoskeleton (21, 32), suggest that levels and functions of HSP27 may be linked to changes in cell cycle events (10). Because cisplatin is more cytotoxic to cells in cycle (35, 36), we investigated the cell cycle kinetics of the overexpressing cells. The population-doubling times increased by 4.3–7.3 h, 17–30% longer than the parental 833K cells. In addition, all the overexpressing clones had slightly fewer cells in S-phase compared with the controls and more cells in G1, the number of cells in G2-M being similar. Whereas these changes in cell cycle kinetics may contribute to the relative resistance of the overexpressing clones to cisplatin, the changes are small compared with the degree of resistance conferred and seem unlikely to make more than a minor contribution to the differences in sensitivity.

The sensitivity of testis tumor cells to DNA-damaging agents is associated with a number of factors, including the low capacity of these cells to repair cisplatin-induced DNA damage, high constitutive levels of topoisomerase II (37), and susceptibility to apoptosis (38). Testis tumor cells rarely have mutations in the p53 gene (39), and this may contribute to their inherent sensitivity to heat and cisplatin and, thus, their curability in the clinic.

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Effect of Overexpression of the Small Heat Shock Protein HSP27 on the Heat and Drug Sensitivities of Human Testis Tumor Cells


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