DNA damage is believed to be the main cause of the antiproliferative effect of cisplatin, a cornerstone agent in anticancer therapy. However, cisplatin can be expected to react also with nucleophiles other than DNA. Using enucleated cells (cytoplasts) we demonstrate here that cisplatin-induced apoptotic signaling may occur independently of DNA damage. Cisplatin-induced caspase-3 activation in cytoplasts required calcium and the activity of the calcium-dependent protease calpain. It is known that calpain activation may be associated with endoplasmic reticulum (ER) stress, suggesting that the ER is a cytosolic target of cisplatin. Consistent with this hypothesis, cisplatin induced calpain-dependent activation of the ER-specific caspase-12 in cytoplasts as well as in intact cells. Cisplatin also induced increased expression of Grp78/BiP, another marker of ER stress. By contrast, the DNA-damaging topoisomerase II inhibitor etoposide did not induce apoptotic signaling in cytoplasts nor ER stress in intact cells. We have thus identified a novel mechanism of action of cisplatin. The results have implications for the understanding of resistance mechanisms as well as the unique efficiency of this drug.

Cisplatin is a widely used chemotherapeutic agent generally recognized as a DNA-damaging drug. The molecular mechanisms that link the formation of DNA adducts to cell death-inducing signaling are not well understood. We have previously reported that cisplatin induces at least two apoptotic signaling pathways. One involves calpain activation and calpain-mediated cleavage of the proapoptotic BH3-only protein Bid. The other one results in MEKK1-dependent modulation of the proapoptotic protein Bak (1, 2). Both pathways contribute to cytochrome c release and subsequent caspase activation.

In aqueous solutions, the chloride ligands of cisplatin are replaced by water molecules generating a positively charged electrophile. This electrophile reacts with nucleophilic sites on intracellular macromolecules to form DNA, RNA, and protein adducts (3). Approximately 1% of intracellular cisplatin reacts with DNA resulting in intra- and interstrand cross-links, with an intrastrand cross-link between adjacent guanines as the most common adduct (4, 5). DNA adducts are considered the key toxic lesions induced by cisplatin; however, some studies have not shown a clear correlation between DNA adducts and cisplatin cytotoxicity (6, 7). The potential contribution of cisplatin-induced RNA or protein damage to cytotoxicity has not been examined in this respect (8).

This prompted us to investigate the ability of cisplatin to induce apoptosis independently of DNA damage, and we here report the ability of cisplatin to induce apoptosis in enucleated cells. The cisplatin response was also found to involve endoplasmic reticulum (ER) stress. Altogether, we have here identified an apoptotic pathway induced by cisplatin independently of its DNA-damaging activity. This novel mechanism of action may contribute to the understanding of the causes of sensitivity and resistance to cisplatin.

**EXPERIMENTAL PROCEDURES**

**Cells**—The human melanoma cell line 224 and two variants of the colon cancer cell lines HCT116 (wt and p53-deficient) (9) were used. The cells were maintained at 37 °C in 5% CO₂ in RPMI medium supplemented with fetal calf serum (10%), L-glutamine, penicillin, and streptomycin.

**Cytoplast Preparation**—The cells were harvested, resuspended in 12.5% Ficoll containing complete medium supplemented with cytochalasin B (10 μg/ml), and incubated for 30 min at 37 °C. Three ml of this cell suspension was layered onto a density gradient prepared in ultracentrifuge tubes with the following layers: 2 ml of 25%, 2 ml of 17%, 0.5 ml of 16%, and 0.5 ml of 15% Ficoll. The gradient was prepared in complete medium supplemented with 10 μg/ml of cytochalasin B and pre-equilibrated in a CO₂ incubator overnight. The cells were then centrifuged in a prewarmed (32 °C) Beckman SW41 swing bucket rotor for 60 min at 25,000 rpm. The resulting enucleated cytoplasts were collected at the interface between the 16 and 17% Ficoll layers and were then washed with medium and allowed to recover for 2 h before drug treatment.

The purity of the cytoplast preparation was determined by resuspending cytoplasts in PBS containing digitonin (50 μg/ml) and labeling with 5 μg/ml propidium iodide (PI). After 10 min of incubation at room temperature, fluorescence was monitored using the FL2 channel on a FACS Calibur flow cytometer.

**Western Blot Analysis**—Cell extract proteins (30 μg) were resolved by SDS-PAGE and transferred onto a polyvinylidene difluoride membrane for Western blotting. The following antibodies were used: anti-caspase-12 (1: 250, a kind gift from Dr. J. Yuan), anti-Grp78/BiP (1:500; BD Transduction Laboratories), and anti-Bid (1:1,000; Molecular Probes, Inc.). Tubulin was used as an internal standard for loading.

**Assessment of Caspase-3 and DEVDase Activity**—After treatment cells were harvested, washed with PBS, fixed in paraformaldehyde (0.25%, 5 min), washed three times with PBS, and incubated for 60 min with a fluorescein isothiocyanate-conjugated antibody recognizing active caspase-3 (Pharmingen). The antibody was diluted 1:50 in PBS containing digitonin (50 μg/ml). After incubation, the cells were washed with PBS, and fluorescence was monitored using the FL1 channel of a FACS Calibur flow cytometer.

DEVDase activity was assessed using the fluorogenic Ac-DEVD-AMC substrate (Casape AC Assay, Promega Life Science). The harvested cells

**Nucleus-independent Apoptotic Signaling**

Cisplatin Induces Endoplasmic Reticulum Stress and Nucleus-independent Apoptotic Signaling*
Cisplatin Induces Nucleus-independent Apoptosis—224 human melanoma and HCT 116 human colon cancer cells were enucleated as described and treated with cisplatin to investigate whether cisplatin can induce nucleus-independent apoptosis. The purity of the cytoplast preparation was determined by staining digitonin-permeabilized cytoplasts with PI and analyzing the sample by flow cytometry. As shown in Fig. 1A (panel I), intact cells demonstrate a 10-fold higher PI fluorescence than cytoplasts, allowing analysis of these two populations separately, by way of electronic gating.

Apoptosis was assessed as activation of caspase-3 using an antibody that specifically recognizes active caspase-3. After treatment with 15 and 20 μM cisplatin for 16 h, the cytoplast preparations were analyzed for PI fluorescence and active caspase-3. In untreated samples, the cut-off for activated caspase-3 was set immediately to the right of the cell/cytoplast population (Fig. 1A). After cisplatin treatment, 43 and 48% of the 224 cytoplasts, respectively, showed activation of caspase-3 (Fig. 1B). 224 cells harbor mutated p53. To confirm that cisplatin-induced apoptosis is independent of p53 status, we compared the effect of cisplatin on wt and p53−/− HCT 116 cytoplasts, respectively. Similar levels of induction of caspase-3 activation were observed in wt and p53−/− cytoplasts after treatment with cisplatin (Fig. 1, C and D).

Bak is a proapoptotic Bcl-2 family protein involved in cytochrome c release from mitochondria. We have previously found that cisplatin induces a proapoptotic conformational modulation of Bak in 224 cells (1). This modulation is assessed with an antibody recognizing a specific N-terminal epitope that is exposed only when Bak is in its activated, proapoptotic form. To determine whether cisplatin can induce nucleus-independent activation of Bak, we examined conformational modulation of Bak in cisplatin-treated cytoplasts. As shown in Fig. 2A, cisplatin induces activation of Bak in 224 cytoplasts. However, this activation is weaker compared with Bak activation in intact 224 cells. Weak Bak activation was also observed in HCT 116 p53 wt and p53-deficient cytoplasts (Fig. 2B).

We have previously shown that cisplatin induces cleavage of the proapoptotic BH3-only protein Bid to its active form tBid (2). tBid is in turn involved in cytochrome c release from mitochondria in both the extrinsic (11, 12) and intrinsic proapoptotic pathways (13, 14). Cisplatin-induced Bid cleavage was compared with 20 μM cisplatin for 16 h. The shift to the right in the dot plot represents an increase in active-caspase-3 immunofluorescence. In B-D, the results are shown as percentages of cells or cytoplasts with activated caspase-3.

**RESULTS**

**Cisplatin Induces ER Stress and DNA-independent Apoptosis**

Upon induction of apoptosis, the proapoptotic Bak protein undergoes a conformational change that exposes an otherwise inaccessible N-terminal epitope (10). In the present study, we have used the same antibody that was shown to specifically recognize this epitope (mouse monoclonal antibody against amino acids 1–52 of Bak; Oncogene Research Products; number AM03, clone TC100). Using a fluorescein isothiocyanate-conjugated secondary antibody, the increases in accessibility of the epitope were monitored by flow cytometry as earlier described (1). The data are presented as fold increases in immunofluorescence from control levels.

**Flow Cytometric Analysis of Bak-associated Immunofluorescence**

The fluorescence produced upon cleavage of the labeled substrate is proportional to the caspase activity in the sample.
therefore examined also in 224 cytoplasts, and the results show that Bid is indeed cleaved (Fig. 2).

Caspase-3 Activation in Cytoplasts Is Blocked by a Calpain Inhibitor and a Calcium Chelator—As we have reported, cisplatin-induced Bid cleavage is carried out by calpain (2). To investigate whether calpain is involved in nucleus-independent apoptosis, we studied the effect of the calpain inhibitor calpeptin on caspase-3 activation in enucleated 224 cells. Cotreatment with calpeptin was found to block cisplatin-induced caspase-3 activation by approximately half (Fig. 3A).

An increase in intracellular calcium is required for calpain activation. Accordingly, cisplatin-induced calpain activation in 224 cells is calcium-dependent (2). Because increased intracellular calcium was also observed in cisplatin-treated enucleated 224 cells (not shown), we examined the effect of the calcium chelator BAPTA-AM on caspase-3 activation in cisplatin-treated cytoplasts. As shown in Fig. 3B, cotreatment with BAPTA-AM inhibited caspase-3 activation by ~60%.

Cisplatin Induces ER Stress in 224 Cells and Cytoplasts—The ER participates in regulation of cellular responses to stress and alterations in calcium homeostasis (15, 16). Caspase-12 is an ER-specific caspase that is activated by ER stress and that specifically participates in ER stress-induced apoptosis (17).

Cisplatin has been indicated as a protease responsible for activation of caspase-12 (18).

The finding that cisplatin induces increased cytosolic calcium and calpain activation suggested that the ER might be a non-nuclear target of cisplatin. The ability of cisplatin to induce ER stress was assessed as activation of caspase-12, reflected in cleavage of 60-kDa procaspase-12. This cleavage was significant at 4 h after cisplatin treatment and was confirmed at 8 h (Fig. 4A). Cleavage was furthermore blocked by calpeptin and by BAPTA-AM (Fig. 4A). Cleavage of caspase-12 was also observed in cytoplasts after 4 and 16 h (Fig. 4B).

Grp78 (glucose-regulated protein 78) is an ER chaperone protein that is up-regulated by ER stress (15, 16). To confirm the ability of cisplatin to induce ER stress, we examined expression of this protein in 224 cells a 2.6-fold increase in Grp78 protein expression was seen at 16 h after cisplatin treatment (Fig. 5A). Induction of Grp78 expression was confirmed by flow cytometry (Fig. 5B) and was not affected by the caspase inhibitor zVAD-fmk (Fig. 5C).

Cisplatin has been shown to induce production of reactive oxygen species (ROS) (20, 21) that have been reported as important mediators of the stress response in many cell types (22). We have previously observed that pretreatment of 224 cells with the ROS scavenger N-acetyl cysteine (NAC) inhibits cisplatin-induced mitochondrial depolarization and nuclear...
fragmentation by ~60% (not shown). However, NAC failed to inhibit calpain activation in cisplatin-treated cells (not shown); thus, cisplatin-induced apoptosis also involves events that are not ROS-dependent. To investigate the possible involvement of oxidative stress in ER stress, we examined the expression of Grp78 in cells treated with cisplatin in the presence or absence of NAC. As shown in Fig. 5C, the presence of NAC did not affect up-regulation of Grp78 levels after cisplatin treatment. This indicates that oxidative stress is not involved in the induction of ER stress by cisplatin.

Apoptosis induced by ER stress involves downstream activation of caspase-3. To investigate whether Grp78 induction correlates with caspase-3 activation, both events were studied simultaneously in cisplatin-treated 224 cells and cytoplasts at the indicated time points. The results are shown as fold increases in Grp78-associated immunofluorescence.

Etoposide-induced Apoptosis Requires Nuclear Events—To demonstrate the specificity of cisplatin in inducing nucleus-independent apoptosis, we treated 224 cytoplasts with etoposide. This is also a DNA-damaging drug, but as a topoisomerase II-inhibitor it has a different mechanism of action than cisplatin. Etoposide failed to induce caspase-3 activation in enucleated cells (Fig. 7A), and thus, in contrast to cisplatin, the effect of etoposide is dependent on an effect on DNA. Furthermore,
etoposide did not have any effect on ER, because no up-regulation of Grp78 (Fig. 7B) nor caspase-12 activation (Fig. 7C) was observed in etoposide-treated cells.

**DISCUSSION**

Cisplatin is a broadly active cytotoxic anticancer drug. In aqueous solutions, the molecule is rendered highly reactive and reacts with nucleophilic sites on intracellular macromolecules. The role of cisplatin adducts on proteins and/or RNA in cisplatin-induced apoptosis is at present unclear. Instead, it is generally accepted that DNA is the critical target of cisplatin, due to the ability of nucleus-containing cells to induce expression of protective proteins in response to cisplatin-induced DNA damage rather than by ER stress. The lower Bak activation in 224 cytoplasts than in intact cells, Bak activation in 224 cytoplasts may show enhanced sensitivity to cisplatin (23–25).

We show here that cisplatin is able to induce proapoptotic signaling and caspase-3 activation in enucleated cells (cytoplasts). Cytoplast preparations also contain a small amount of intact cells with nuclei, which were treated in the same way as cytoplasts, including incubation with cytochalasin B and gradient centrifugation. This population of intact cells was used to directly compare levels of caspase-3 and Bak activation in cytoplasts and intact cells. Higher caspase-3 activation induced by cisplatin was observed in cytoplasts than in intact cells in both 224 and HCT 116 cell lines. This increased activity may be due to the ability of nucleus-containing cells to induce expression of protective proteins in response to cisplatin-induced stress, e.g. Hsp70 (heat shock protein 70) or XIAP (X-linked inhibitor of apoptosis protein). Hsp70 can block apoptosis by interfering with proteins involved in the execution phase of apoptosis such as protease activating factor-1 (28) and apoptosis inducing factor (29). XIAP blocks apoptosis by inhibiting active caspase-3 and caspase-9 (30).

Although the cisplatin-induced caspase-3 activity was higher in cytoplasts than in intact cells, Bak activation in 224 cytoplasts was only slightly increased compared with the 2.5-fold induction of Bak activity in 224 cells. A possible explanation is that Bak activation is predominantly dependent on MEKK1-mediated signaling and that this pathway may be activated by DNA damage rather than by ER stress. The lower Bak activa-

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*Fig. 6. Correlation between caspase-3 activation and Grp78 levels. 224 cells were treated with 20 or 30 μM cisplatin for 16 h and 20 h. Digitonin-permeabilized cells were double-stained with antibodies against active caspase-3 and Grp78, respectively, for FACS analysis. The values in each upper left corner represent the percentages of cells in this quadrant. Active caspase-3 was monitored using fluorescein isothiocyanate-conjugated antibody (all x axes), and the percentage of cells showing activation of caspase-3 is also indicated. The levels of Grp78-associated immunofluorescence (all γ axes) are also shown as median values. Panel a, untreated cells; panel b, 20 μM cisplatin, 16 h; panel c, 30 μM cisplatin, 16 h; panel d, 20 μM cisplatin, 20 h; panel e, 30 μM cisplatin, 20 h.*

*Fig. 7. Etoposide-induced apoptosis requires nuclear events. A, no caspase-3 activation was observed in etoposide-treated cytoplasts. 224 cells and cytoplasts were treated with the indicated doses of etoposide for 16 h. Caspase-3 activity was assessed by flow cytometry. The results are presented as percentages of cells with activated caspase-3. B, etoposide failed to induce expression of Grp78. 224 cells were treated with 15 μM etoposide for 16 h. The levels of Grp78 were examined by Western blotting. C, no cleavage of procaspase-12 was seen in etoposide-treated cells. 224 cells were treated with 15 μM etoposide for 4 and 8 h, and extracts were made for Western blotting. The numbers represent relative levels of protein assessed by laser densitometry.*

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2 A. Mandic, J. Hansson, S. Linder, and M. C. Shoshan, unpublished results.
tion seen in cytoplasts might instead represent activation of the calpain-Bid pathway, which we have shown to be distinct from the MEKK1 pathway (2). Bid has been reported to stimulate formation of Bak oligomer pores in the mitochondrial membrane (31). Because cleavage and activation of Bid was found in 224 cytoplasts, we suggest that Bid-mediated modulation of Bak might be responsible for the slight activation observed in 224 and HCT 116 cytoplasts.

Calpains are a family of cytosolic cysteine proteases, and their activation is preceded by increased levels of cytosolic calcium. We have previously found that increased cytosolic calcium and calpain activation are early events in cisplatin-induced apoptosis and have also presented evidence for calpain-mediated cleavage of Bid in cisplatin-treated 224 cells (2). Here we have shown that these events may occur independently of DNA damage.

These findings also suggested that the ER might be the non-nuclear target of cisplatin. The ER plays an important role in maintenance of intracellular calcium homeostasis, protein synthesis, post-translational modifications, and proper folding of proteins as well as their sorting and trafficking. Alterations in calcium homeostasis and accumulation of unfolded proteins in the ER cause ER stress. A variety of agents, including chemical toxicants, oxidative stress, inhibitors of protein glycosylation, calcium ionophores, and other agents that alter calcium homeostasis can all induce ER stress followed by cell death (16).

To investigate the involvement of the ER in cisplatin-induced apoptosis, we examined activation of caspase-12 and up-regulation of Grp78. Apoptosis induced by ER stress has been shown to involve calpain-mediated activation of caspase-12 (18). Caspase-12 is localized to the ER and may be activated by disruption of calcium homeostasis and accumulation of excess proteins in ER but not by membrane- or mitochondria-targeted apoptotic signals (17). Murine caspase-12 is a member of the ICE (interleukin-1β converting enzyme) subfamily of caspases. The amino acid sequence of caspase-12 shows high homology with human casapse-4 (48% identity) and caspase-5 (45% identity). The monoclonal antibody used in the present study has been shown to detect a human counterpart of caspase-12 and to locate it to the ER in HeLa cells (17). The same antibody has also been used for detection of caspase-12 cleavage in human epithelial cells (32).

This is the first report to show the involvement of ER stress, specifically seen as caspase-12 activation and up-regulation of Grp78, in cisplatin-induced apoptosis. We also present evidence for nucleus-independent activation of caspase-12. In accordance with calpain-mediated activation of caspase-12, both calpeptin and BAPTA were able to block cisplatin-induced cleavage of caspase-12 in 224 cells. Although caspase-7 has also been reported to cleave procaspase-12 (19), it is probably not involved in our system, because no DEVDase was detected at 4 h post-treatment, when caspase-12 was already cleaved.

Cisplatin has been shown to induce oxidative stress in variety of cell lines. As expected, cotreatment of 224 cells with the ROS scavenger NAC resulted in decreased nuclear fragmentation and mitochondrial depolarization. However, NAC did not have any effect on the induction of Grp78, showing that ROS production is not required for ER stress. This is supported by the findings that calpain is likely involved in caspase-12 activation and that NAC did not block calpain activation.

For unknown reasons, basal expression levels of Grp78 varied widely in the 224 cells. However, cisplatin induced a general increase in Grp78 expression, and this effect was independent of caspase-12 and caspase-3 activation, because the pan-caspase inhibitor zVAD-fmk did not affect it. At 16 h, caspase-3 was activated in cells with high Grp78 expression. Interestingly, there was also a population with high Grp78 expression but no caspase-3 activation (Fig. 6, upper left quadrant). The size of this population is reduced to below control levels only at the later time point and with the higher dose. This observation is in accordance with the antiapoptotic or protective effect of Grp78, which possibly has some specificity against drugs inducing calcium depletion from the ER (16). With this antiapoptotic action, Grp78 may well contribute to resistance against cisplatin, which may now be counted among the ER-active anti-cancer drugs. The basal level of Grp78 is up-regulated in many tumors (16), but to our knowledge, the relationship between Grp78 levels and cisplatin sensitivity/resistance has not been studied.

In contrast to cisplatin, etoposide, which is also a DNA-damaging drug but which achieves its effect by inhibition of topoisomerase II, did not induce caspase-3 activation in cytoplasts. Etoposide thus requires nuclear events to induce apoptosis. Furthermore, etoposide-induced apoptosis does not involve ER stress because it did not induce caspase-12 activation in 224 cells or cytoplasts, nor did it lead to increased Grp78 expression in 224 cells in summary, we here demonstrate a novel mechanism of action for cisplatin, a chemotherapeutic agent hitherto regarded as a typical DNA-damaging agent. Cisplatin is here shown to induce apoptosis in the absence of DNA damage, and the ER is likely its non-nuclear target. We propose that the ability to activate two, rather than a single, major pathways to apoptosis makes cisplatin so generally efficient as an anti-cancer agent. Lastly, we believe that our findings will lead to a re-evaluation of resistance-determining factors for cisplatin and possibly to new, improved treatment strategies to overcome resistance.

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