Glucocorticoids Inhibit Cell Death in Ovarian Cancer and Up-regulate Caspase Inhibitor cIAP2

Ingo B. Runnebaum and Ansgar Brüning

Abstract

Purpose: Almost all patients with epithelial ovarian cancer receive chemotherapy and, concurrently, the synthetic steroid hormone dexamethasone to alleviate the side effects. This study aims to test the impact of steroid hormones on the apoptosis of epithelial ovarian cancer cells and to identify its mediators.

Experimental Design: Tumor cell lines from 19 patients with advanced epithelial ovarian cancer were analyzed for glucocorticoid receptor, estrogen receptor, progesterone receptor, and androgen receptor expression. Cells were incubated with corresponding steroid hormones at serum-equivalent doses in hormone-depleted medium. Apoptosis was induced by application of tumor necrosis factor–related apoptosis-inducing ligand or staurosporine and determined by poly(ADP-ribose)polymerase cleavage and cell survival. Microarray with 8K cDNA chips including apoptosis-relevant genes was used to study genes regulated by glucocorticoids.

Results: In cell culture, tumor necrosis factor–related apoptosis-inducing ligand–induced apoptosis in OV-MZ-30 and OV-MZ-31 cells was reduced after treatment with dexamethasone or cortisol, but not with estradiol, progesterone, or androstenedione. Microarray analysis revealed a 7-fold up-regulation of the caspase inhibitor cIAP2 by dexamethasone in OV-MZ-30 and OV-MZ-31 cells. cIAP2 up-regulation by glucocorticoids was confirmed by RT-PCR and Western blot analysis in OV-MZ-30, OV-MZ-31, OV-CAR3, and SK-OV-3 cells. Down-regulation of cIAP2 expression by small interfering RNA sensitized SK-OV-3 cells to apoptosis inducer staurosporine. Under clinical conditions, treatment with dexamethasone was associated with significant up-regulation of cIAP2 in the ascites cells.

Conclusions: Activation of the glucocorticoid receptor in epithelial ovarian cancer cells caused an antiapoptotic effect associated with the enhanced cellular expression level of cIAP2. Dexamethasone pretreatment of epithelial ovarian cancer patients receiving apoptosis-inducing chemotherapy raises questions about a negative effect on antitumor efficacy.

Plasma levels of steroid hormones such as estrogens, androgens, progesterone, and the cellular expression level of the corresponding hormone receptors can be factors promoting the development of several solid tumors including ovarian and breast cancer (1–3). The expression of the estrogen receptor in breast cancer is a well-known example and its pharmacologic inhibition by (selective) antiestrogens is extensively studied for breast cancer treatment as well as for its prevention (4, 5). Less is known about the impact of steroid hormones on the development of ovarian cancer. Contradictory studies on hormone replacement therapy regarding ovarian cancer risk have been presented (6, 7).

Besides sex hormone receptors, the glucocorticoid receptor is another steroid hormone receptor with an effect on cancer cells. The synthetic glucocorticoid dexamethasone has been shown to increase resistance to chemotherapeutic drugs and radiation therapy in cells from solid cancer (8–12). This finding is of particular clinical significance because exogenously applied dexamethasone is a routine pretreatment used to attenuate the side effects of chemotherapy or irradiation, such as nausea and emesis (13, 14). In epithelial ovarian cancer, except from the rare Federation Internationale des Gynaecologistes et Obstetrices stage IA with histopathologic grading G1, all patients receive either an adjuvant or first-line platinum-based chemotherapy, in advanced stages combined with paclitaxel. Patients routinely receive dexamethasone, mostly two oral doses of 20 mg each, 12 and 6 hours before chemotherapy.

The effect of glucocorticoids on apoptosis of epithelial ovarian cancer cells has not been studied yet. Particularly, little is known about the effect of endogenously produced glucocorticoids on apoptosis. Resistance against endogenously produced apoptotic factors is one hallmark of cancer development as cancer cells permanently need to escape apoptosis-inducing agents produced and exhibited by cells of the
immune system (15). Members of the tumor necrosis factor family, such as CD95L, tumor necrosis factor, or tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) in either secreted or membrane-bound forms are such well-known endogenously produced apoptosis inducers with antitumor effect (16–18).

For a better understanding of the role of steroid hormones and steroid hormone receptors in ovarian cancer, we analyzed the expression of the estrogen receptor, progesterone receptor, androgen receptor, and glucocorticoid receptor in epithelial ovarian cancer cell lines and tested the influence of endogenous and synthetic steroid hormones on ovarian cancer cell survival.

Materials and Methods

**Cells and cell culture.** The mammary cancer cell line, MCF-7, and the ovarian carcinoma cell lines, SK-OV-3 and OV-CAR-3, are American Type Culture Collection–available cell lines. The other ovarian cancer cell lines, OV-MZ-1a, 2a, 5, 6, 9, 12, 15, 19, 20, 21, 22, 26, 27, 30, 31, 32, and 33 have previously been established as primary cancer cell lines (19) and used at passage numbers between 22 and 61. Cells were cultured in DMEM supplemented with 10% FCS and antibiotics at 37°C in a humidified atmosphere with 5% CO₂. All cell culture reagents were from Invitrogen, Karlsruhe, Germany, except for hormone-depleted (charcoal-stripped) FCS, which was from Biochrom, Berlin, Germany. Cell counting was done with a hemocytometer.

**Treatment of cells with steroid hormones.** 17β-Estradiol, progesterone, 4-androstene-3,17-dione, and dexamethasone (9α-fluor-16α-methylprednisolone) were from Sigma, Schnelldorf, Germany, and kept in ethanolic stock solutions. Cell culture experiments were done with DMEM supplemented with 10% hormone-depleted FCS (Biochrom), done in duplicate and repeated at least twice.

**Induction and determination of cell death.** To induce cell death, OV-MZ-30 cells and OV-MZ-31 cells at a density of 5 × 10⁶ cells/well were treated with 5 ng/mL TRAIL (Peprotech, London, United Kingdom). After 24 hours of incubation, cells were washed with PBS and the remaining cells were trypsinized and calculated with a Neubauer cell counting chamber (hemocytometer) using trypan blue exclusion for identification of viable cells.

**RT-PCR analysis.** RT-PCR analysis was done essentially as described (19). Primer pairs were (forward/reverse in 5′ to 3′ orientation) cagggtctggctgctctgcgatgctgc for estrogen receptor-α (483 bp, 31 cycles), ctctcaaggttggatcactgcagagatgat for androgen receptor (342 bp, 32 cycles), gattcagaaggacccagagtcgtcctgcag for progesterone receptor (533 bp, 34 cycles), ctctcagaccccacctctcctcgg for glucocorticoid receptor-α (547 bp, 31 cycles), and accaagaaggaggtgggatggggt for cIAP2 siRNA into 10⁶ SK-OV-3 cells in 272 mmol/L sucrose, 10 mmol/L Tris buffer (pH 7.4). Stable cell clones were selected by application of 400 μg/mL G418 for 2 weeks to the cell culture dishes before subcloning.

**Results**

**Expression of estrogen, progesterone, androgen, and glucocorticoid receptor in ovarian cancer cells.** A panel of 19 human ovarian cancer cell lines was screened by RT-PCR analysis for the expression of estrogen receptor, progesterone receptor, androgen receptor, and glucocorticoid receptor. The established mammary cancer cell line MCF-7, known to be positive for expression of all of these receptors (22), was used for control. In RT-PCR analysis, MCF-7 cells proved to be positive for estrogen receptor expression (Fig. 1), whereas only 2 (SK-OV-3...
and OV-MZ-33) out of 19 ovarian cancer cell lines were identified to express the estrogen receptor (Fig. 1). Expression of progesterone, androgen, and glucocorticoid receptor was found at highly differing expression levels in most ovarian cancer cell lines tested (Fig. 1).

**Dexamethasone mediates an antiapoptotic effect in ovarian cancer cells.** Ovarian cancer cell lines, OV-MZ-30 and OV-MZ-31, were highly sensitive to TRAIL. To test for the influence of steroid hormones on ovarian cancer cell apoptosis, OV-MZ-30 and OV-MZ-31 cells were incubated with either 10 nmol/L estradiol, 30 nmol/L progesterone, 10 nmol/L androstenedione, or 100 nmol/L dexamethasone for activation of the corresponding steroid hormone receptors. Cells were treated with or without 5 ng/mL TRAIL and the number of viable cells was counted after an additional 24-hour incubation (Fig. 2A and B). TRAIL treatment induced significant signs of apoptosis (e.g., membrane blebbing; data not shown) eventually leading to cell death and detachment. In OV-MZ-30 and OV-MZ-31 cells pretreated with dexamethasone, a significantly higher number of cells survived application of TRAIL (Fig. 2A and B).

No enhanced cell survival after TRAIL application was found in OV-MZ-30 and OV-MZ-31 cells treated with either estradiol, progesterone, or androstenedione (Fig. 2A and B). In OV-MZ-33 or OV-MZ-27 cells lacking glucocorticoid receptor expression (Fig. 1), none of the tested steroid hormones induced changes in TRAIL sensitivity, even in the estrogen receptor–positive OV-MZ-33 cell line (data not shown).

**Antiapoptotic effect of endogenous steroid hormones.** The serum equivalent of low-dose dexamethasone, when applied in clinical protocols, is in the range of 10 to 200 nmol/L (8). Whereas dexamethasone is a synthetic drug applied during cancer treatment, the human body produces a panoply of endogenous glucocorticoid hormones, varying in concentration and composition depending on age, sex, circadian rhythm, and external factors. We tested the effect of the main endogenous glucocorticoid hormones on TRAIL-mediated apoptosis by applying concentrations similar to mean plasma levels described (ref. 23; 18.5 nmol/L corticosterone, 24.5 nmol/L cortisone, 195.5 nmol/L hydrocortisone/cortisol). To consider the known variations that can occur in the serum levels of these hormones, a 5-fold higher concentration of these hormones was additionally included. Among the endogenous glucocorticoids tested, a significant inhibitory effect at serum-equivalent levels against TRAIL-mediated apoptosis was observed mainly for hydrocortisone (cortisol)-treated OV-MZ-31 cells (Fig. 2C). Results were similar for OV-MZ-30 cells (data not shown). The previously pronounced antiapoptotic effect of serum-equivalent doses of hydrocortisone prompted us to test for the effects of further applications of dexamethasone. Additional application of dexamethasone to OV-MZ-31 cells incubated with endogenous glucocorticoid hormones further enhanced the resistance of OV-MZ-31 cells against TRAIL-induced apoptosis (Fig. 2D). However, a maximum level for cellular

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**Fig. 2.** Cell proliferation and cell survival of hormone-treated ovarian cancer cells. A total of 2.5 × 10⁴ cells of the ovarian cancer cell lines OV-MZ-30 (A) or OV-MZ-31 (B–D) were incubated for 24 hours in 24-well cell culture plates supplemented with 10 nmol/L estradiol, 30 nmol/L progesterone, 10 nmol/L androstenedione, or the designated glucocorticoids at the indicated concentrations. Cells were then treated with or without 5 ng/mL TRAIL and the number of viable cells was counted after a further 24 hours of incubation.
protection by glucocorticoids was observed that could not be further exceeded (Fig. 2D). Testing different concentrations of dexamethasone, the antiapoptotic effect reached its maximum at a concentration of 200 nmol/L of dexamethasone and could not be exceeded even when dexamethasone concentrations were increased up to 1 μmol/L (data not shown).

**Microarray analysis revealing cIAP2 as the main antiapoptotic factor modulated by dexamethasone in ovarian cancer cells.** To identify genes responsible for the antiapoptotic effect in dexamethasone-treated ovarian cancer cells, microarray analysis of dexamethasone-treated OV-MZ-30 and OV-MZ-31 cells was done. A cDNA library of 7,768 human cDNAs (see Materials and Methods) spotted in duplicate on glass coverslips was tested. Genes found to be up-regulated in duplicate with an arbitrary cutoff level of ≥4-fold are summarized in Table 1 for OV-MZ-30 and for OV-MZ-31 cells. In both OV-MZ-30 and OV-MZ-31 cells, a 7- to 8-fold up-regulation of cIAP2 (synonyms, “inhibitor of apoptosis protein-1”, HIAP1, MIHC) was found. cIAP2 is known to function as a direct inhibitor of caspases 3 and 9 enzyme activity (24). Additional genes found to be significantly and reproducibly up-regulated by dexamethasone in both OV-MZ-30 and OV-MZ-31 cells were metallothioneins and CI100, both proteins known to be regulated by glucocorticoids (25, 26). Up-regulation of cIAP2 by dexamethasone could be confirmed by RT-PCR analysis as shown for OV-MZ-30 and OV-MZ-31 cells (Fig. 3A), as well as for SK-OV-3 cells, tested and included as an additional ovarian cancer cell line (Fig. 3A). Band density quantification analysis calculating cIAP2/β-actin ratios revealed up-regulation of cIAP2 mRNA by 197% in SK-OV-3 cells, by 137% in OV-MZ-30 cells, and by 40% in OV-MZ-31 cells.

**Dexamethasone enhanced expression of cIAP2 on the protein level.** To test whether enhanced cIAP2 mRNA expression results in enhanced cIAP2 protein expression, we did Western blot analysis of dexamethasone-treated OV-CAR-3, SK-OV-3, OV-MZ-30, and OV-MZ-31 cells (Fig. 3B). An enhanced protein level of cIAP2 could be observed in all tested dexamethasone-treated ovarian cancer cells (Fig. 3B). For quantitation, the expression level of cIAP2 protein as determined by image analysis was related to the corresponding β-actin protein expression level as an internal standard and calculated as cIAP2/β-actin ratios (Fig. 3C). Comparison of cIAP2 mRNA

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and protein expression levels among the tested ovarian cancer cells in the absence of dexamethasone, or under conditions of dexamethasone treatment (Fig. 3A and B), suggest a close relation between cIAP2 mRNA expression level and protein expression level. Using a polyclonal XIAP antibody, XIAP expression was detectable in OV-CAR-3 cells, but was not detectable or only faintly detectable in the other epithelial ovarian cancer cells (Fig. 3B). Unexpectedly, in OV-CAR-3 cells, XIAP expression seemed to be reduced after dexamethasone treatment (Fig. 3B). Expression of cIAP1 protein could not be detected by Western blot analysis (data not shown).

Glucocorticoid treatment resulted in reduced PARP cleavage after TRAIL treatment. As cIAP2 is a specific inhibitor of apoptosis-mediating caspase 3 (24), we analyzed the cleavage of the caspase 3 substrate PARP, which is cleaved by caspase 3 from the 115 kDa protein into an inactive 85 kDa fragment by activated caspase 3. No cleavage of PARP could be detected in OV-MZ-30 or OV-MZ-31 cells in the absence of TRAIL (data not shown). TRAIL treatment resulted in the formation of the 85 kDa PARP fragment in OV-MZ-30 or OV-MZ-31 cells (Fig. 4A). Under the influence of dexamethasone, TRAIL-induced cleavage of PARP was observed to be less in both OV-MZ-30 and OV-MZ-31 cells (Fig. 4A).

siRNA-mediated down-regulation of cIAP2 sensitized SK-OV-3 cells to staurosporine-mediated apoptosis. To show that the expression level of cIAP2 is a crucial factor in the apoptotic event of ovarian cancer cells, a siRNA approach was done in order to reduce the cIAP2 expression level of ovarian cancer cells. As the primary ovarian cancer cell lines OV-MZ-30 and OV-MZ-31 did not reveal sufficient clonogenic potential, stable cIAP2 siRNA-expressing cell clones were generated from the widespread and readily clonogenic SK-OV-3 cell line. After electroporation of the pGB cIAP2 siRNA plasmid into SK-OV-3 cells, four stable, neomycin-resistant cell clones were generated (designated, si1-4; Fig. 4B), which was proven to exhibit a significantly lower cIAP2 protein expression level than the parental SK-OV-3 cell line (par., Fig. 4B). As SK-OV-3 cells were resistant to TRAIL treatment even at high concentrations (data not shown), cells were incubated with 500 ng/mL staurosporine, which, in contrast to paclitaxel (taxol), has been shown to induce apoptosis in SK-OV-3 cells via caspase 3 activation (27). Parental SK-OV-3 cells were sensitive to staurosporine treatment as shown in Fig. 4D, still, sensitivity to staurosporine was enhanced in all cell clones with reduced cIAP2 expression level (Fig. 4C). Wilcoxon test analysis (SPSS 12.0, SPSS, Munich, Germany) revealed data to be statistically significant ($P = 0.012$).

Enhanced expression of cIAP2 in the ascites of an ovarian cancer patient treated with dexamethasone. We investigated whether clinically applied doses of dexamethasone could also increase cIAP2 expression in cells taken directly from ascites of an ovarian cancer patient. The chemo-naïve patient tested received dexamethasone for palliation to reduce ascites

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**Fig. 3.** RT-PCR and Western blot analysis of cIAP2 mRNA and protein expression in ovarian cancer cells. A, the ovarian cancer cell lines SK-OV-3, OV-MZ-30, and OV-MZ-31 were treated for 16 hours with or without 100 nmol/L dexamethasone as indicated and subjected to semiquantitative RT-PCR analysis for the expression of cIAP2 and β-actin. β, the ovarian cancer cell lines OV-CAR-3, SK-OV-3, OV-MZ-30, and OV-MZ-31 were treated for 24 hours with or without 100 nmol/L dexamethasone as indicated and subjected to Western blot analysis for the expression of cIAP2 and β-actin. C, expression levels of cIAP2 as shown in (B) and that of an identical experiment (not shown) were determined by image analysis (Bio-Rad Quantity One, Bio-Rad, Munich, Germany) and related to the corresponding β-actin expression level as an internal standard (C).
production. Ascites was first collected from the ovarian cancer patient 2 hours before oral administration of dexamethasone (4 mg Fortecortin tablet). Ascites was again collected after 6 and 8 hours following dexamethasone application. Cells from the ascites were collected and prepared for semiquantitative RT-PCR analysis (Fig. 5). RT-PCR analysis of ascites cells revealed a significant up-regulation of cIAP2 after dexamethasone treatment. Up to 8 hours following dexamethasone application, cIAP2 was expressed at a significantly higher level than before dexamethasone treatment (Fig. 5).

**Discussion**

Despite the widespread application of dexamethasone as a supportive drug in ovarian cancer therapy, no studies on the effect of glucocorticoids on apoptosis and apoptotic pathways have yet been published for epithelial ovarian cancer cells. Our study shows that glucocorticoids of either exogenous or endogenous origin cause an antiapoptotic effect in epithelial ovarian cancer cells, accompanied by up-regulation of cIAP2 expression. cIAP2 is a cytosolic caspase inhibitor, interfering with the proteolytic activity of caspases 3 and 9 (28). Caspase 3 is the effector caspase in apoptosis and can be activated by irradiation, chemotherapeutics, or members of the tumor necrosis factor family (18, 29–31). cIAP2 was identified in this study because of its established and well-known function as an antiapoptotic protein. It cannot be excluded that other factors are involved in the antiapoptotic effect of glucocorticoids in ovarian cancer. We observed significant up-regulation of metallothionein proteins by dexamethasone (Table 1). The primary function of metallothioneins as metal ion-binding proteins (25) does not seem to be directly related to apoptosis.
and cell survival. Still, ribozyme-mediated down-regulation of metallothionein 2a has been shown to induce apoptosis in prostate and ovarian cancer cells (32), and overexpression of metallothioneins was identified as a negative prognostic marker in melanomas (33). We further observed up-regulation of CL100 (MKP-1) by glucocorticoids (Table 1). Although the primary function of this protein phosphatase is not known to be that of an apoptosis inhibitor, Wu et al. (12) showed that overexpression of CL100 could exert an antiapoptotic effect in human epithelial ovarian cancer cells. In that study, microarray analysis for antiapoptotic genes regulated by dexamethasone in breast cancer cells was done and identified CL100 (MKP-1) and SGK-1 (glucocorticoid-inducible protein kinase) as two factors involved in the antiapoptotic effect of glucocorticoids in breast cancer cells. As cIAP2 was not on the annotation list of the tested Affymetrix HG-U95Av2 chips (www.affymetrix.com), it was not possible to analyze the effect of glucocorticoids on cIAP2 expression in MDA-MB-231 breast cancer cells as done in the abovementioned study (12). Still, cIAP2 is up-regulated by glucocorticoids even in breast cancer cells, as analyzed by our group using the MCF7 breast cancer cell line.1 In our microarray study, done on OV-MZ-30 and OV-MZ-31 ovarian cancer cells, as well as in the study of Wu et al. (12), no glucocorticoid-induced up-regulation of bcl family members could be observed in ovarian or breast cancer cells, although genes for these proteins were annotated on the used cDNA lists. Notwithstanding, for fibrosarcoma cells, it has been shown that glucocorticoids could increase the bcl-XL level by inducing the transcriptional activation of the bcl-XL promoter (34). A glucocorticoid response element has previously been identified within the cIAP2 promoter region (35) and it was shown that dexamethasone induced cIAP2 expression in A549 lung cancer cells, A172 glioblastoma cells, and in CEM-C7 leukemia T cells (35). The identification of a glucocorticoid-response element in the cIAP2 promoter suggests a direct, primary gene induction effect of glucocorticoids on cIAP2 expression in ovarian cancer. Down-regulation of cIAP2 protein expression or inhibiting its activity could be a very promising means to sensitize cancer cells against chemotherapeutic agents. Recently, a small, cell-permeable molecule that inhibits activity of XIAP and induces apoptosis in leukemia cells was presented (36). Development of such a molecule against cIAP2 could create a promising drug for application in ovarian cancer.

We conclude that the antiapoptotic effect of glucocorticoids on human epithelial ovarian cancer cells is mediated by up-regulation of several cellular factors including cIAP2 with direct antiapoptotic function, and most likely by additional factors such as CL100 and metallothioneins, with secondary anti-apoptotic function.

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1 Unpublished results.
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