Hepatocyte Growth Factor Sensitizes Human Ovarian Carcinoma Cell Lines to Paclitaxel and Cisplatin

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ABSTRACT

The hepatocyte growth factor (HGF) receptor, encoded by the MET oncogene, is expressed in ~70% of human ovarian carcinomas and overexpressed in 30% of cases. Because HGF is known to protect cells from apoptosis, we investigated whether receptor expression modifies ovarian cancer cell response to chemotherapy. The apoptotic effect of the frontline chemotherapeutic drugs paclitaxel and cisplatin on cells treated with HGF was studied. In ovarian cancer cell lines, pretreatment with HGF surprisingly enhances the apoptotic response to low doses of paclitaxel and cisplatin. HGF empowers specifically the intrinsic apoptotic pathway, whereas it protects cells from extrinsic Fas-induced apoptosis. Chemotherapy sensitization is specific for HGF because another growth factor (e.g., epidermal growth factor) increases ovarian cancer cell survival. In nonovarian cancer cell models, as expected, HGF provides protection from drug-induced apoptosis. These data show that HGF sensitizes ovarian carcinoma cells to low-dose chemotherapeutic agents. This suggests that HGF may be used to improve response to chemotherapy in a set of human ovarian carcinomas molecularly classified based on the MET oncogene expression.

INTRODUCTION

The overall growth of a tumor depends on the cooperation between deregulated cell proliferation and impaired programmed cell death (apoptosis). The apoptotic machinery is silently present in all of the cells, and apoptosis is set off by a variety of stimuli during development and adult life, implying a pivotal role of cell death in tissue formation and homeostasis. Because the aberrant proliferation of cancer cells stems directly from their ability to evade apoptosis, a primary aim of cancer therapy is to target or bypass the mechanisms of apoptosis protection in tumor cells (1).

In ovarian cancer, apoptosis is impaired by the antiapoptotic action of several oncoproteins, which include growth factor receptors and other kinases that transduce signals from the membrane to the nucleus (2–4). We and others have demonstrated previously that the MET oncogene-encoded receptor for the hepatocyte growth factor (HGF) is overexpressed in a consistent fraction of ovarian cancers (5, 6). Its ligand, HGF, has been found in ovarian cancer ascitic fluids and in fluid of benign and malignant ovarian cysts (7). HGF elicits a distinctive biological program known as “invasive growth,” which results from the coordinated activation of cell proliferation, survival, and motility together with the degradation of extracellular matrix (8). The orchestration of invasive growth is of paramount importance for organ development during embryogenesis. For instance, mice lacking HGF show impaired organ development and die in utero (9). The deregulation of these processes in cancer onset and progression contributes to HGF-induced tumor growth and invasion (10).

HGF protects cells from programmed cell death in most physiologic and pathologic scenarios. It counteracts apoptosis elicited by a variety of stimuli, including oxidative stress, radiation, growth factor deprivation, anoikis, and chemotherapeutic agents (11–15). Transgenic expression of an activated MET kinase makes liver cells immortalized and resistant to apoptosis (16). The survival role of HGF has been observed in a number of cancer types, such as breast carcinoma, glioblastoma, and leiomyosarcoma cells (11, 17–20). Nonetheless, in some experimental conditions, HGF-mediated cytotoxicity has been reported (21–24).

We have studied the effect of HGF on ovarian cancer cell response to paclitaxel (PTX) and cisplatin (CDDP), the two front-line anticancer agents used in ovarian cancer therapy. We report that HGF surprisingly increases cell sensitivity to apoptosis induced by these drugs.

MATERIALS AND METHODS

Chemicals and Antibodies. PTX and CDDP were from Bristol-Myers Squibb (Rocky Hill, NJ). The caspase inhibitor z-Val-Ala-Asp-fluoromethyl ketone (z-VAD-fmk) was from Bachem (Bubendorf, Switzerland); FITC-conjugated Annexin V was from Boehringer Mannheim (Indianapolis, IN); and tetramethylrhodamine methyl ester (TMRM) was from Molecular Probes (Eugene, OR); all of the other chemicals were from Sigma (St. Louis, MO). CH-11 anti-Fas monoclonal antibody was from Upstate Biotechnology (Lake Placid, NY); anti-poly(ADP-ribose) polymerase and anticaspase-8 antibodies were from PharMingen (San Diego, CA); and anti-lamin B monoclonal antibody was from Oncogene Research (BOSTON, MA). Anti-GADD45, anti-IAP1, anti-IAP2, and anti-activin polyclonal antibodies were from Santa Cruz Biotechnology (Santa Cruz, CA). Recombinant human tumor necrosis factor α (TNF-α) was from PeproTech (Rocky Hill, NJ).

Cell Lines and Apoptosis Induction. Cell lines tested were purchased from American Type Culture Collection (Manassas, VA) and grown as suggested by the provider in media supplemented with 10% fetal bovine serum (Euroclone, Wetherby, United Kingdom) and 2 mM l-glutamine. Experiments were performed with the culture of exponentially growing cells for 48 h with HGF at the concentration of 100 ng/ml, unless otherwise stated, or control medium. Recombinant HGF was obtained from culture supernatant of SF9 cells infected with the baculovirus vector containing the full-size human factor. Pure human recombinant HGF was from R&D Systems (Minneapolis, MN). Apoptosis was induced by adding fresh medium, with or without HGF, supplemented with PTX or CDDP at various concentrations for 72 h. Where indicated, the pan-caspase inhibitor z-VAD-fmk (100 μM) was added 1 h before the induction of apoptosis.

Flow Cytometry Analysis of Apoptosis Induction. Flow cytometry recordings of several independent apoptotic changes were performed by a single-tube analysis, as described previously (25). Briefly, after induction of apoptosis, cells were resuspended in HEPES buffer (10 mM HEPES, 135 mM NaCl, and 5 mM CaCl2) and incubated for 15 min at 37°C in FITC-conjugated Annexin V, TMRM (200 nm), and propidium iodide (PI; 1 μg/ml) to detect phosphatidylserine exposure on the cell surface, mitochondrial inner membrane electrochemical gradient (ΔΨm), and plasma membrane integrity, respectively. Cell morphology changes were analyzed following variations of the forward and side light scatter. Samples were analyzed on a FACSCalibur flow cytometer (Becton Dickinson, San Diego, CA). Data acquisition was per-
formed using CellQuest software (Becton Dickinson), and data analysis was done using WinMDI software. FITC-Annexin V (FL1), TMRM (FL2), and PI (FL3) fluorescent signals were displayed as density plot diagrams. These data were shown as arbitrary units of fluorescence on a logarithmic scale. A quadrant was set on the diagram experiment by experiment, and it was kept constant in all of the conditions of each experiment to indicate the different cell populations. To quantify the degree of mitochondrial depolarization, the geometric mean (Gm) of the TMRM signal was calculated on the histogram window of WinMDI after discriminating apoptotic and nonapoptotic subpopulations with a logical gate tool.

**Western Immunoblot Analysis.** Cytosolic extracts were prepared from cells at 4 °C with 1% NP40 in 135 mM NaCl, 20 mM Tris/HCl (pH 7.5), and 1 mM CaCl₂ in the presence of phosphatase and protease inhibitors (1 mM vanadate, 1 μg/ml leupeptine, 1 μM pepstatine, 1 mM phenylmethylsulfonyl fluoride, and 100 μg/ml soybean trypsin inhibitor). Proteins were separated on SDS-polyacrylamide gels and transferred onto Hybond-C Extra membranes (Amersham, Little Chalfont, United Kingdom) following standard methods. Primary antibodies were incubated 16 h at 4 °C, and horseradish peroxidase-conjugated secondary antibodies were added for 1 h. Proteins were visualized by enhanced chemiluminescence (Amersham).

**Assessment of Apoptotic Nuclear Changes.** Apoptotic nuclear changes were assessed by orange acridine staining and DNA fragmentation analysis. The orange acridine assay was performed on cells plated in 96-well cell culture plates (Costar Corporation, Cambridge, MA). After apoptosis induction, cells were stained for 35–40 s with acridine orange solution and analyzed on a fluorescence microscope equipped with the appropriate filter set. DNA degradation was detected with the terminal deoxynucleotidyltransferase-mediated dUTP nick end labeling (TUNEL) technique using the in situ cell death detection kit (Boehringer Mannheim) following manufacturer’s instructions. These data are presented as cytofluorimetric recordings of fluorescence intensities.

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**Fig. 1.** Hepatocyte growth factor (HGF) effect on apoptosis induction by paclitaxel (PTX) or cisplatin (CDDP). SK-OV-3 (A), TOV-21-G (B), or OV-90 (C) ovarian cancer cells were exposed for 72 h to PTX or CDDP at the reported concentrations. Where indicated, cells were pretreated for 48 h with HGF (100 ng/ml). Representative experiments demonstrating the output of multiparametric fluorescence-activated cell sorter analyses are shown. Diagrams represent Annexin V-FITC versus tetramethylrhodamine methyl ester (TMRM) staining; the percentages of the cell populations in each quadrant are indicated. Cells displaying mitochondrial depolarization are in the lower parts of each plot, whereas cells exposing phosphatidylserine (PS) on their surface are in the right quarters of the diagrams. PI is the percentage of propidium iodide-permeable (i.e., dead) cells.

**Fig. 2.** Dose-response and timing of hepatocyte growth factor (HGF) effects on apoptosis induction by drugs. The effect of HGF on SK-OV-3 ovarian cancer cells is analyzed by flow cytometry in a dose-response assay (A) and by coadministering HGF together with the drugs [paclitaxel (PTX), 5 nM; cisplatin (CDDP), 20 μM] (B). Diagrams and percentages of the different cell populations are indicated as in Fig. 1.
sity on a logarithmic scale versus the normalized number of recorded events. To quantify the degree of DNA fragmentation, the Gm of the terminal deoxynucleotidyltransferase-mediated nick end labeling-FITC signal was calculated on the histogram window of WinMDI after discriminating apoptotic and nonapoptotic subpopulations with a logical gate tool.

**Real-Time PCR.** cDNAs were obtained from total RNA extracted by RNAWIZ reagent (Ambion, Austin, TX) after treating cells for 48 h with HGF (100 ng/ml), PTX (10 nM), or HGF plus PTX or CDDP (after a 48-h preincubation with HGF alone), or from cells in control conditions. Five μg from each RNA sample were reverse transcribed into cDNA with Moloney murine leukemia virus reverse transcriptase (Promega, Madison, WI). Quantitative real-time reverse transcription-PCR was performed using SYBR green with TaqMan assay (Applied Biosystems, Foster City, CA). Forward and reverse primers were designed using Primer Express v1.5 software (Applied Biosystems) from sequences provided by SuperArray Inc. (Bethesda, MD) for each gene of interest. Each PCR reaction was optimized to ensure that a single band of the appropriate length was amplified. Preliminary experiments were done with each primer pair to determine the primer concentrations that yielded the greatest amount of specific product with melting temperature separable from primer-dimer temperature. The PCR cycling conditions were performed for all of the samples as follows: 10 min at 95°C and 40 cycles for the melting (95°C for 15 s) and annealing/extension (60°C for 1 min) steps. Each assay was done in triplicate and included a "no-template" control per gene-specific primer tested. The comparative CT method was used to quantify the expression of each gene in treated versus control cells using 18S rRNA as a normalization control (26).

**RESULTS**

**HGF Pretreatment Consistently Increases the Apoptosis Response to PTX or CDDP.** We selected the ovarian cancer cell lines SK-OV-3, TOV-21G, NIH:OVCAR-3, and OV-90, which are sensitive to PTX and CDDP (Ref. 27 and data not shown) and respond to HGF by phosphorylation of the MET oncogene-encoded HGF receptor (Refs. 5, 28 and data not shown).

To perform a detailed investigation of chemotherapeutic agent-triggered apoptosis, we previously set up a cytofluorimetric technique...
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HGF Specifically Enhances the Caspase-Dependent Apoptotic Program Induced by PTX or CDDP. The apoptotic process activated by chemotherapeutic agents is composed of a triggering phase, which leads to the functional impairment of mitochondria and the consequent activation of proteases termed caspases, followed by execution steps in which caspases mediate cell dismantling and eventually cause DNA to break into fragments. Caspases are mutually activated by proteolytic processing, whereas their substrates are functionally silenced by the cleavage (see Fig. 8). As depicted in Fig. 3A, SK-OV-3 cell pretreatment with HGF before CDDP or PTX increased the cleavage into the expected fragments of caspase-8 and of poly-(ADP-ribose) polymerase and lamin B, nuclear targets of caspase-3/7 and caspase-6, respectively. DNA fragmentation caused either by PTX or CDDP, with a net increase of the measured apoptotic features (compare the first and second rows of the panels in Fig. 1). The number of residual viable cells was confirmed by trypan blue exclusion (data not shown).

HGF enhanced chemotherapeutic drug-induced apoptosis of ovarian cancer cells in a dose-dependent fashion (Fig. 2A). Notably, this sensitization required pretreatment with HGF because its coinubcation with the drugs was ineffective (Fig. 2B).

Specificity of the Proapoptotic Effects of HGF. We investigated whether apoptosis sensitization by HGF was common to cells of cancer types other than ovarian carcinoma by studying the colon carcinoma COLO 741 and HT-29 cells, the gastric carcinoma GTL-16 cells, and the breast carcinoma MDA-MB-231 and MDA-MB-435 cells. In all of these cells, preincubation with HGF had a survival effect, counteracting the apoptosis triggered by PTX or CDDP (Fig. 4 and data not shown). HGF-mediated sensitization to chemotherapy observed in ovarian carcinoma cells could be the result of nonspecific, growth factor-dependent activation of the cell death machinery. This was not the case, however, because another growth factor (namely, epidermal growth factor) had a survival effect on cells exposed to PTX or CDDP (Fig. 5A).

Apoptosis signal transduction can use either intrinsic pathways, which activate caspases downstream to mitochondrial function dysregulation as PTX or CDDP do, or extrinsic pathways, exemplified by (see “Materials and Methods” and Ref. 25) for the simultaneous measurement of the following apoptotic hallmarks: decrease of ΔΨm, cell shrinkage, increase in granularity, exposure of phosphatidylserine at cell surface, and plasma membrane permeabilization to PI.

In response to either PTX or CDDP, ovarian cancer cells entered the apoptotic program as assessed by changes in all of the aforementioned parameters (Fig. 1 and data not shown). HGF induced either no (in SK-OV-3 cells) or slight (in TOV-21G and OV-90 cells) apoptotic changes by itself. In all of the ovarian cancer cell lines, it caused unexpectedly a marked sensitization to the subsequent treatment with PTX or CDDP, with a net increase of the measured apoptotic features (compare the first and second rows of the panels in Fig. 1). The number of residual viable cells was confirmed by trypan blue exclusion (data not shown).
a receptor-initiated apoptotic signal (see Fig. 8). We stimulated the ovarian cancer cell lines with a recombinant TNF-α and an agonist anti-Fas antibody, which trigger prototypical extrinsic pathways. In these conditions, HGF preincubation displayed a survival effect (Fig. 5, B and C) similar to that observed with a wide-range caspase inhibitor, abolishing all of the apoptotic changes (Fig. 5D). This indicates that HGF inhibits an early step of the extrinsic apoptosis cascade, possibly the juxtamembrane caspase activation (see Fig. 8).

Our observations indicate collectively that HGF specifically exerts an enhancing role on ovarian cancer cell apoptosis induced by chemotherapeutic treatment and that this effect is restricted to the activation of intrinsic apoptotic pathways.

HGF Increases the Cytotoxicity Induced by PTX or CDDP. To confirm that apoptosis induction eventually led to cell death, we studied nuclear morphologic changes triggered by chemotherapeutic drugs with or without HGF. We found that in SK-OV-3 cells, a 48-h preincubation with HGF made ovarian cancer cells more sensitive to PTX or CDDP in a dose-dependent fashion, as shown by DNA condensation and nuclear fragmentation. HGF alone did not induce cell death, although it did cause cell scattering (Fig. 6A). Cell death increase was more evident with low doses of chemotherapeutic agents (Fig. 6B). The same result was confirmed in TOV-21G cells (Fig. 6C) and in the other ovarian cancer cell lines (data not shown).

HGF Effects on the Transcription of Apoptosis-Related Genes Induced by PTX or CDDP. Because pretreatment was required to sensitize ovarian cancer cells to chemotherapeutic agents, we asked whether HGF could act on the apoptosis machinery by modulating gene transcription.

To test this hypothesis, we studied the transcriptional regulation of apoptosis-related genes using real-time quantitative reverse transcription-PCR. These included genes of the Bcl-2 family, BIRC genes, which encode inhibitors of apoptosis (BIRC/IAPs), components of the DNA repair machinery, and genes functionally related to the TNF receptor family.

As reported in Fig. 7A, we found that DNA repair family and BIRC/IAPs gene transcripts are modulated in SK-OV-3 ovarian cancer cells by drugs and drugs plus HGF. In particular, expression of GADD45α was induced by CDDP and increased further, up to 15-fold, by pretreatment with HGF. We verified that transcriptional changes matched variations in protein levels by comparing real-time reverse transcription-PCR results with Western blot analysis. The expression of the GADD45α protein consistently was increased markedly by HGF treatment before CDDP and PTX administration. BIRC/IAPs RNA changes did not result in comparable protein variations (Fig. 7B).

DISCUSSION

In this report, we demonstrate that HGF, the ligand of the receptor tyrosine kinase encoded by the MET oncogene, sensitizes ovarian carcinoma cells to CDDP- and PTX-induced apoptosis through a caspase-dependent apoptotic pathway. It is worth noting that HGF does not induce apoptosis by itself, thus indicating that its role is to facilitate apoptosis triggered by the chemotherapeutic agents. The use of different cell death assays allowed us to determine that HGF affects execution steps of the apoptosis program by increasing caspase activity downstream to mitochondria depolarization. HGF specifically

Fig. 6. Hepatocyte growth factor (HGF) effect on nuclear changes of ovarian cancer cells treated with cisplatin (CDDP) or paclitaxel (PTX). SK-OV-3 (A and B) and TOV-21G (C) ovarian cancer cells were exposed to 1-10 nM PTX or to 5-20 μM CDDP, and nuclear changes were assessed by orange acridine staining. Where indicated, cells were preincubated for 48 h with 100 ng/ml HGF and then treated with the chemotherapeutic agents. A, representative fields of stained cells. B and C, percentage of nuclei showing morphologic changes. Each data point represents the mean (± SD) of three replicates in a representative experiment.

Fig. 7. Regulation of apoptosis-related genes and proteins by hepatocyte growth factor (HGF), paclitaxel (PTX), or cisplatin (CDDP). SK-OV-3 ovarian cancer cells were exposed for 48 h to PTX (10 nM), CDDP (20 μM), or HGF (100 ng/ml) or were preincubated for 48 h in HGF before treatment with CDDP or PTX. Results of quantitative real-time reverse transcription-PCR analysis on DNA repair genes, BIRC/IAPs family genes, control genes (alkaline phosphatase and phospho-glycerol kinase; top), Bcl-2 family genes, and tumor necrosis factor receptor-related genes (bottom) are displayed in A. Values are shown in a linear scale as fold changes versus control conditions. B, changes in protein levels for products of some of the genes reported in A are studied by Western immunoblot assay. Cells are incubated in the same conditions as in A.
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![Diagram of apoptotic pathways](image)

**Fig. 8.** Proposed effects of hepatocyte growth factor (HGF) on apoptotic pathways in ovarian cancer cells. Chemotherapeutic treatment sets off apoptosis by causing mitochondrial dysfunction (mitochondrial depolarization and release of apoptogenic molecules). This leads to caspase activation and the consequent cell dismantling, whose hallmark is phosphatidylserine exposure on the cell surface, additional mitochondrial depolarization, cleavage of caspase targets, DNA fragmentation, and eventually cell death. Steps after mitochondrial dysfunction are enhanced by HGF. Engagement of the Fas receptor immediately recruits and activates caspases in a multimolecular complex on the inner side of plasma membrane. In this case, HGF inhibits apoptosis progression.

empowers the intrinsic apoptotic pathway and impairs the Fas-mediated extrinsic apoptosis cascade. These observations show that the effect of HGF on the mechanism(s) of apoptosis is exerted on early regulatory steps (Fig. 8).

HGF-mediated sensitization to drug-induced apoptosis in ovarian cancer cells is a novel finding. As a rule, HGF protects normal cells and a variety of cancer cells from apoptosis (11–15, 17–20). Nonetheless, HGF had been shown to induce apoptosis in a sarcoma cell line and in liver carcinoma models (21–24). Furthermore, HGF induces death of ovarian surface epithelial cells when extracellular matrix or intercellular contacts are lacking (29, 30). However, in all of these cases, HGF had a cytotoxic effect *per se*. Thus, HGF specifically regulates the apoptosis program, depending on the cell type and setting. Accordingly, we show that HGF pretreatment sensitizes ovarian cancer cells treated with PTX or CDDP to apoptosis, whereas, as expected, it protects cells derived from several other cancer types.

One could hypothesize that HGF sensitizes cells to apoptosis by driving proliferation. Overriding cell cycle checkpoints in a damaged cell could spur cells to activate a cell death program to curtail dangerous proliferation (31). However, this is not the case because HGF does not affect the G1/M cell cycle arrest induced by the drugs (data not shown). Moreover, we observe that treatment with epidermal growth factor, which stimulates ovarian cell proliferation, inhibits apoptosis induction. This is in line with data reporting that epidermal growth factor overexpression is correlated with poor prognosis in ovarian tumors because it inhibits chemotherapy-mediated apoptosis, and indicates that growth factors can affect differentially the survival response in the same cell model (32).

Because HGF-dependent sensitization to drugs required long-term exposure, we reasoned that apoptosis enhancement by HGF could be coupled to transcriptional regulation of apoptosis-related genes. Interestingly, HGF given with the chemotherapeutic drugs strongly increased the expression of GADD45A at either mRNA or protein level. GADD45A usually is increased in response to genotoxic stress and participates in nucleotide excision repair (33, 34). Notably, it can sensitize different tumors to undergo apoptosis after genotoxic stimuli, and GADD45A-null mice develop tumors, including ovarian carcinomas, at an increased rate. We did not detect a transcriptional response with Bcl-2 family and TNF receptor-related genes. This was not surprising because expression of these molecules is not even changed in SK-OV-3 cells made resistant to PTX by long-term exposure to the drug (35). In our experiments, transcription of the BIRC5/IAPs family of apoptosis inhibitors was modulated, whereas proteins did not change. However, it must be noted that kinetics of modulation can be different and that IAPs undergo multiple levels of regulation, either transcriptional or post-transcriptional (36).

The primary intracellular targets of CDDP and PTX are distinct: CDDP binds to DNA, forming adducts that block replication and/or prevent transcription; PTX stabilizes microtubules, leading to suppression of cytoskeleton dynamics and inhibition of the mitotic spindle (37, 38). Both compounds kill tumor cells by triggering apoptosis, and the combination of CDDP and PTX has led to improved response rates and prolonged median survival in ovarian cancer (39, 40). Unfortunately, the onset of drug resistance makes these therapies ineffective in the long term, and ovarian cancer remains one of the most lethal malignancies in Western countries. With the aim of overcoming resistance, innovative therapeutic strategies are under current investigation (41). These include modulation of growth factor receptor transduction pathways that restore cancer cell apoptosis (42, 43).

We show that a molecular classification of ovarian carcinoma cells (with or without MET expression) identifies a set of ovarian carcinomas that could be responsive to the combined treatment with HGF (or HGF derivatives) and low doses of conventional anticancer agents. These findings are relevant to a large number of ovarian carcinomas because we and others have observed that ~70% of ovarian carcinomas express MET, and its expression level increases from 3-fold to >50-fold in nearly 30% of cases (5, 6). Therefore, HGF or HGF derivatives could be used to improve response to chemotherapy in ovarian carcinomas (44). This possibility is particularly intriguing because it is well known that HGF protects normal tissues from the cytotoxic effects of chemotherapeutic agents.

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REFERENCES

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