Src Tyrosine Kinase and Multidrug Resistance Protein-1 Inhibitions Act Independently but Cooperatively to Restore Paclitaxel Sensitivity to Paclitaxel-Resistant Ovarian Cancer Cells

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Abstract

Src tyrosine kinase has been found to be overexpressed in both mouse and human ovarian cancer cells as well as in human primary ovarian cancers. Furthermore, Src inhibition sensitizes ovarian cancer cells to chemotherapeutic agents such as paclitaxel and cisplatin. Interestingly, Src inhibition has also been shown to resensitize paclitaxel-resistant ovarian cancer cells. The paclitaxel-resistant human (CaOV3TaxR) and mouse (ID8TaxR) ovarian cancer cell lines express large amounts of the multidrug resistance-1 (MDR-1) protein compared with the paclitaxel-sensitive parent cell lines. Src inhibition had no effect on MDR-1 protein expression. Furthermore, Src inhibition did not affect MDR-1 function as determined by rhodamine 123 and paclitaxel uptake or retention. Coinhibition of both Src and MDR-1 synergistically enhanced paclitaxel-induced cytotoxicity in paclitaxel-resistant ovarian cancer cell lines. Inhibition of Src enhanced microtubule stabilization in paclitaxel-resistant ovarian cancer cells treated with paclitaxel without affecting expression of β-tubulin isotypes and resulted in multipolar spindle formation and apoptosis. These results show that Src inhibition restores paclitaxel sensitivity to paclitaxel-resistant ovarian cancer cells by an MDR-independent mechanism, possibly by decreasing the critical intracellular concentration at which paclitaxel induces tubulin stabilization and bundling. Src tyrosine kinase may provide a viable target for therapeutic intervention in drug-resistant ovarian cancer.

Introduction

The standard first-line therapy for ovarian cancer includes tumor debulking followed by chemotherapy treatment with paclitaxel, platinum-based agents, or combinations of both (1). Unfortunately, even in patients in whom there is an initial positive clinical response, the development of recurrent drug-resistant ovarian cancer is a common outcome (2), leading to poor 5-year survival rates of below 30% (3).

The development of multidrug (chemotherapeutic) resistance is most probably multifactorial. Several mechanisms have been proposed, including increased multidrug resistance-1 (MDR-1)/P-glycoprotein expression (4, 5). MDR-1 is an ATP-dependent drug efflux pump that confers resistance to a great many drugs, including taxanes such as paclitaxel. Cells made resistant to paclitaxel invariably up-regulate MDR-1 expression. Another possible mechanism of paclitaxel resistance is a change in profile of β-tubulin expression, favoring up-regulation of β-subunit III isotype (6, 7). Cancer cells may also develop resistance through the induction of survival pathways that allow cells to survive prolonged G2-M arrest. This has been shown with the activation and stabilization of the antiapoptotic and mitotic checkpoint factor survivin (8). We have previously shown that inhibition of Src tyrosine kinase sensitizes human and mouse ovarian cancer cells to chemotherapeutic agents such as paclitaxel and cisplatin (9). Furthermore, Src inhibition restores sensitivity to microtubule-disrupting agents in paclitaxel-resistant ovarian cancer cells (10). Interestingly, Src inhibition also restores sensitivity to other classes of chemotherapeutic agents, such as cisplatin, to which the paclitaxel-resistant cells are cross-resistant (9, 10).

The mechanism by which Src inhibition restores paclitaxel sensitivity is at present not clear. The current study was undertaken to determine whether MDR-1 was involved in mediating paclitaxel resistance and resensitization and whether Src inhibition altered MDR expression or function. MDR-1 protein expression was greatly increased in paclitaxel-resistant cells; however, Src inhibition had no effect on MDR-1 expression or function and, in fact, acted synergistically with MDR-1 inhibition in restoring paclitaxel sensitivity. Src inhibition seems to decrease the critical intracellular concentration at which paclitaxel induces tubulin stabilization and apoptosis.

Materials and Methods

Reagents. All liquid media and Lipofectamine 2000 transfection reagent were purchased from Invitrogen Life Technologies (Carlsbad, CA). Rhodamine 123, Oregon Green-labeled paclitaxel, 4,6-diamidino-2-phenylindole (DAPI), and Alexa 488–conjugated goat anti mouse antibody were from Molecular Probes (Eugene, OR). An antibody directed against MDR-1 was from Oncogene Sciences (Boston, MA). Antibodies to β-tubulin and β-actin were from Santa Cruz Biotechnology (Santa Cruz, CA). Src inhibitors 4-amino-5-(4-chlorophenyl)-7-[(f-butyl)pyrazolo[3,4-d]pyrimidine (PP2) and SU6656, MDR-1 inhibitor verapamil, and paclitaxel were obtained from Calbiochem (La Jolla, CA). Vectashield mounting medium was purchased from Vector Laboratories (Burlingame, CA). Enhanced chemiluminescence (ECL) Western blotting detection reagents were purchased from Amersham Life Science Incorporated (Arlington Heights, IL), Cisplatin, antibodies to individual β-tubulin isotypes (II, III, and IV), and all other reagents were purchased from Sigma (St. Louis, MO).

Cell culture. The development of ID8 and ID8TaxR mouse ovarian cancer cells has been previously described (9, 11). Both cell lines were cultured in DMEM supplemented with 4% fetal bovine serum (FBS), insulin (10 μg/mL), and...
transferrin (5 μg/mL), sodium selenite (7 ng/mL), and HEPEs (15 mmol/L). The human ovarian cancer cell line CaOV3 was obtained from the Lombardi Cancer Center Tissue Culture Shared Resource and maintained in DMEM supplemented with FBS (10%) and HEPEs (15 mmol/L). The CaOV3TaxR paclitaxel-resistant cell line was derived from the CaOV3 cell line as previously described. Both CaOV3TaxR and ID8TaxR cells were maintained in 1 μmol/L paclitaxel.

**Relative cell viability.** Cell viability at the end of cytotoxicity assays was determined by direct cell counts. Briefly, cells were seeded at 20,000 cells per well in 24-well plates and allowed to attach overnight. After attachment, media were removed and replaced with fresh full-growth media and treatments were initiated (minimum of four wells per treatment). Following the treatment period, detached dead cells were removed, cells were washed, and the remaining cells were then detached by trypsin digestion; cells were counted using a hemocytometer. For statistical analyses, control values were set to 100%. Treatment effects were analyzed by ANOVA for differences between individual means and compared by Fisher’s protected least significant difference test. Experiments were repeated at least three times.

The combination index was used to determine if drug combinations acted antagonistically, additively, or synergistically (12). The combination index is defined by the equation combination index = D1 / (DX)1 + D2 / (DX)2, where D1 equals the concentration of drug 1 necessary to produce a particular effect (e.g., 50% cytotoxicity) in combination; (DX)1 is the concentration of the same drug required to produce the same effect on its own; D2 is the concentration of the second drug necessary to produce the particular effect in combination; and (DX)2 is the concentration of drug 2 required to produce the same effect on its own. Combination index > 1 indicates antagonism; combination index = 1 indicates an additive effect; and combination index < 1 is indicative of synergism.

**Rhodamine 123 uptake and retention.** MDR-1 drug efflux function was determined in ID8 and ID8TaxR cells by rhodamine 123 uptake and retention assays (13). Cells were seeded at 20,000 cells per well in 24-well plates and allowed to attach overnight. After attachment, media were removed and replaced with fresh full-growth media and treatments were added for a 30-minute preincubation period (minimum of four wells per treatment). After 30 minutes, media were replaced with fresh media containing treatments and rhodamine 123 (0.1 mg/mL). Cells were then incubated at 37°C for 1 hour. For uptake studies, cells were placed on ice at the end of the 1-hour rhodamine 123 uptake incubation period, washed twice with ice-cold Hanks buffer, and intracellular rhodamine 123 was extracted with 0.1% SDS in PBS. Fluorescence was measured at λex = 485 nm/λem = 530 nm using a fluorescence microplate reader. For retention assays, following the 1-hour rhodamine 123 uptake incubation, media were removed, cells were washed twice with fresh media, and then fresh media with respective treatments were added and cells were incubated for a further 2 hours. One set of wells without treatment was immediately washed and rhodamine 123 was extracted following the 1-hour uptake incubation to serve as control uptake. At the end of the 2-hour efflux incubation period, intracellular rhodamine 123 was determined as outlined above. For comparison, the intracellular rhodamine 123 at the end of the efflux period was compared with the intracellular rhodamine 123 at the end of the uptake period (100% uptake) for each individual cell line. Experiments were repeated three times.

**Immunoblotting.** For immunoblotting, cells were seeded on glass coverslips in six-well culture plates. After the treatment period (described in Results), cells were fixed with 4% paraformaldehyde for 10 minutes at room temperature. Cells were permeabilized with 0.1% NP40 in PBS for 20 minutes at room temperature. Coverslips were blocked with 10% preimmune serum (in PBS) from the species in which the secondary antibody was raised. Following blocking, coverslips were incubated with primary antibody (1:200) in PBS-1% normal serum at room temperature for 2 hours. Negative controls consisted of coverslips incubated with preimmune immunoglobulin G. Coverslips were then washed extensively with PBS, incubated with an Alexa 488–conjugated secondary antibody (1:200) for 2 hours at room temperature, washed in PBS, counterstained with DAPI (0.1 μg/mL PBS) for 15 minutes, and then washed with PBS. Coverslips were mounted with Vectashield mounting medium and sealed. Cells were visualized by laser-scanning confocal microscopy.

**Immunofluorescence.** For immunofluorescence, cells were seeded on glass coverslips in six-well culture plates. After the treatment period, cells were fixed with 4% paraformaldehyde for 10 minutes at room temperature. Cells were permeabilized with 0.1% NP40 in PBS for 20 minutes at room temperature. Coverslips were blocked with 10% preimmune serum (in PBS) from the species in which the secondary antibody was raised. Following blocking, coverslips were incubated with primary antibody (1:200) in PBS-1% normal serum at room temperature for 2 hours. Negative controls consisted of coverslips incubated with preimmune immunoglobulin G. Coverslips were then washed extensively with PBS, incubated with an Alexa 488–conjugated secondary antibody (1:200) for 2 hours at room temperature, washed in PBS, counterstained with DAPI (0.1 μg/mL PBS) for 15 minutes, and then washed with PBS. Coverslips were mounted with Vectashield mounting medium and sealed. Cells were visualized by laser-scanning confocal microscopy.

**Results**

**Multidrug resistance-1 protein is up-regulated in human (CaOV3TaxR) and mouse (IDSTaxR) ovarian cancer cells.** We have developed two paclitaxel-resistant ovarian cancer cell lines: IDS TaxR (mouse) and CaOV3TaxR (human) ovarian cancer cells (10). Both cell lines are resistant to >2 μmol/L paclitaxel and neither is paclitaxel dependent. Both lines show cross-resistance to microtubule-disrupting agents (e.g., colchicine) as well as other chemotherapeutic agents, such as cisplatin, which act by tubulin-independent mechanisms. A common mechanism by which cells become drug-resistant is by the up-regulation of ATP-dependent drug efflux pumps such as MDR-1. Gene array profiling comparing IDS (paclitaxel-sensitive) versus ID8 TaxR (paclitaxel-resistant) mouse ovarian cancer cells found that of the 281 and 299 genes that increased in expression across two arrays, the MDR-1 message increased the most across both arrays (2.61- and 2.91-fold, respectively). To verify increased protein expression, immunoblot analysis was done as outlined above following removal of soluble tubulin (0.1% Triton X-100 extraction for 20 minutes at 37°C) and then fixation with 4% paraformaldehyde. Immunofluorescence was done with the β-tubulin isotype-specific antibodies listed above.
paclitaxel sensitivity was examined by exposing CaOV3 TaxR and ovarian cancer cells to paclitaxel. To examine MDR-1 function, rhodamine 123 uptake and efflux were examined in ID8 and ID8TaxR cells. ID8TaxR cells took up and retained less rhodamine 123 (Fig. 1B) than the ID8 parent cell line; however, Src inhibition with either PP2 or SU6656 had no effect on rhodamine 123 uptake or retention compared with nontreated ID8 or ID8TaxR cells. These results suggest that Src inhibitors do not simply interfere with or act as competitive inhibitors of MDR-1 function or other ATP-cassette transporters. We have also used paclitaxel labeled with an Oregon Green fluorescent tag (Taxol-OG). Both ID8 and ID8TaxR cells label with Taxol-OG (Fig. 1C), demonstrating that despite the presence of MDR-1, ID8TaxR cells can still take up and retain some paclitaxel. Treatment with Src inhibitors did not alter the ability of cells to label with Taxol-OG (data not shown). Collectively, these data show that the effect of Src inhibition is not mediated through MDR-1 protein expression. Similar results were observed in CaOV3TaxR cells (data not shown).

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**Inhibitions of Src and multidrug resistance-1 act synergistically in restoring paclitaxel sensitivity to paclitaxel-resistant ovarian cancer cells.** The ability of MDR-1 inhibition to restore paclitaxel sensitivity was examined by exposing CaOV3TaxR and ID8TaxR cells to paclitaxel or a combination of both paclitaxel and verapamil, an inhibitor of ATP-dependent drug efflux pumps. As expected, treatment of cells with verapamil resensitized paclitaxel-resistant ovarian cancer cells to paclitaxel (1 μmol/L) in a dose-dependent manner (Fig. 2A). Src inhibition with the Src inhibitor PP2 also resensitized both cell lines in a dose-dependent manner (Fig. 2B), confirming previous results (9, 10). The ED50 concentrations for verapamil and PP2 were then used in combination. Treatment of cells with both verapamil and PP2 synergistically resensitized cells to paclitaxel (Fig. 2A and B, boxes). The combination indices were 0.91 and 0.73 for CaOV3TaxR and ID8TaxR cells, respectively (combination index < 1.0 is considered synergistic; ref. 12). Furthermore, treatment of cells with verapamil and PP2 resensitized paclitaxel-resistant ovarian cancer cells over a range of paclitaxel concentrations (Fig. 2C).

**β-Tubulin isotype expression and microtubule stabilization in paclitaxel-resistant ovarian cancer cells.** Because Src and MDR-1 inhibitions both acted to restore paclitaxel sensitivity in both mouse and human ovarian cancer cell lines, we next determined the ratio of monomeric Triton X-100 (0.1%)-soluble tubulin to Triton X-100-insoluble tubulin polymers under various treatment conditions. Treatment of ID8TaxR cells with PP2 was associated with a shift of tubulin to the Triton X-100-insoluble fraction in response to paclitaxel (0.25 and 1.0 μmol/L; Fig. 3A and B). Treatment of cells with 1 μmol/L verapamil was associated with...
with a similar but less dramatic shift of tubulin to the insoluble fraction. Treatment with verapamil, PP2, and paclitaxel (0.25 \( \mu \text{mol/L} \)) induced a dramatic shift of tubulin from the Triton X-100–soluble to the Triton X-100–insoluble fraction, indicating microtubule stabilization.

It has been suggested that a possible mechanism for paclitaxel resistance is through altered expression of \( \beta \)-tubulin isotypes, favoring up-regulation of the \( \beta \)-subunit III isotype (6, 7). To determine if there were alterations in \( \beta \)-tubulin isotype expression in our paclitaxel-resistant cell lines, tubulin isotype was determined from total protein in mouse (ID8) and human (CaOV3) paclitaxel-sensitive ovarian cancer cells by immunoblot analysis with antibodies specific for \( \beta \)-tubulin isotypes I, III, and IV and compared with their respective paclitaxel-resistant sublines. Unexpectedly, the only significant change in \( \beta \)-tubulin isotype expression was a...
decrease in βIII in CaOV3TaxR cells in comparison with the paclitaxel-sensitive CaOV3 parental line (Fig. 3C). Comparing ID8 and ID8TaxR cells, there was no similar change in βIII expression. Additionally, comparing paclitaxel-sensitive and paclitaxel-resistant cell lines, there were no significant changes in the expression of either βI or βIV isotype (Fig. 3C). This was further confirmed by the gene array profiling comparing ID8 versus ID8TaxR cells, which failed to detect differences in β-tubulin isotype message expression (data not shown).

We next determined the changes in Triton X-100–insoluble β-tubulin isotypes under various treatment conditions. Combination treatment with paclitaxel and Src inhibition was associated with increased insoluble βIII subunit in both ID8TaxR and CaOV3TaxR cells compared with treatment with paclitaxel or Src...
inhibition alone (Fig. 4). Insoluble βI increased marginally in both CaOV3TaxR and ID8TaxR cells in response to combination treatment whereas βIV showed little effect in response to combination treatment in CaOV3TaxR cells. Interestingly, the tubulin βIV isotype showed a significant increase in the insoluble fraction in response to paclitaxel alone in ID8TaxR cells.

The unexpected decrease in βIII-tubulin expression in CaOV3TaxR cells in comparison with the paclitaxel-sensitive CaOV3 parental cell line prompted us to examine localization of insoluble polymeric β-tubulin isotypes. Insoluble polymeric βIII-tubulin was localized in both the cytoplasm and nucleus of CaOV3 (Fig. 5A) and ID8 cells (Fig. 5C). In comparison, there was a dramatic loss of cytoplasmic insoluble βIII-tubulin in CaOV3TaxR cells (Fig. 5B). There was a similar but less dramatic decrease in cytoplasmic localization in ID8TaxR cells. Both insoluble βI and βIV tubulin isotypes were found to be primarily cytoplasmic during interphase in all cell types (e.g., Fig. 6). All three β-tubulin isotypes localized to the normal mitotic spindle and to central spindle components during anaphase in control and paclitaxel-treated CaOV3TaxR cells (Fig. 6). Interestingly, βI-tubulin and βIV-tubulin isotypes localized prominently to the disrupted, multipolar spindle (multiple asters) of apoptotic paclitaxel-treated CaOV3TaxR cells in which Src had been inhibited. In contrast, polymeric insoluble βIII-tubulin did not show the same strong localization.

Figure 5. Decreased cytoplasmic localization of insoluble βIII tubulin in paclitaxel-resistant ovarian cancer cells. Human (CaOV3; A) and mouse (ID8; C) ovarian cancer cells and their respective paclitaxel-resistant (CaOV3TaxR and ID8TaxR, B and D, respectively) derivatives were plated on glass coverslips overnight. Soluble tubulin was extracted and then cells were fixed. Immunofluorescence was done with an antibody specific for βIII-tubulin and an Alexa 488-conjugated secondary antibody. DNA was stained with DAPI. B, inset, CaOV3TaxR cells in which soluble βIII-tubulin was not extracted before fixation.
spindle localization in apoptotic cells, suggesting βIII-tubulin might not be involved in the mitotic arrest induced by paclitaxel and Src inhibition. Similar observations were made with ID8TaxR cells (results not shown).

Discussion

Chemoresistance or multidrug resistance is a major contributor to the high mortality rate of recurrent ovarian cancer (2, 3). It is likely that several different mechanisms are involved in the acquisition and maintenance of multidrug resistance, including up-regulation of ATP-dependent drug efflux pumps, such as MDR-1, increased tolerance to DNA damage, increased drug metabolism, changes in microtubule isotype expression, and β-tubulin mutations. Resistance to taxanes, microtubule-stabilizing agents commonly used in the treatment of ovarian cancer, is probably mediated by all of the above mechanisms, with the possible exception of increased tolerance to DNA damage. We have developed both mouse (ID8TaxR) and human (CaOV3TaxR) paclitaxel-resistant ovarian cancer cell lines through exposure to increasing sublethal concentrations of paclitaxel (9, 10). Gene array analysis showed that MDR-1 message increased more than any other message in ID8TaxR cells across two separate gene arrays (26.1- and 29.1-fold increase) compared with ID8 paclitaxel-sensitive cells. The present study confirms the increased message expression is accompanied by increased MDR-1 protein. CaOV3TaxR cells also showed a dramatic increase in MDR-1 protein expression, thus providing one potential mechanism of taxane resistance.

We have previously shown that inhibition of Src tyrosine kinase resensitizes paclitaxel-resistant ovarian cancer cells (9, 10). It is possible that small-molecule kinase inhibitors, such as PP2, may serve as substrates for MDR-1 (15), thus acting as competitive inhibitors for paclitaxel efflux in paclitaxel-resistant, MDR-1-overexpressing ovarian cancer cells. Several lines of evidence in the present study do not support this possibility: Src inhibition

**Figure 6.** Src inhibition promotes multipolar spindle formation in response to paclitaxel in paclitaxel-resistant ovarian cancer cells. Paclitaxel-resistant CaOV3TaxR cells were plated on glass coverslips and treated as indicated for 6 hours. Soluble tubulin was extracted and then cells were fixed. Immunofluorescence was done with antibodies specific for the indicated β-tubulin isotype and an Alexa 488-conjugated secondary antibody. DNA was stained with DAPI. Note the localization of β-tubulin isotypes to central spindle components during anaphase in paclitaxel-treated cells (A, C, and E, arrows). Also note fragmented apoptotic nuclei (arrowheads) in combination-treated cells and strong signal for βIII-tubulin (B) and βIV-tubulin (F) isotypes in the multipolar spindle development.
MDR-1 combined inhibitions acted synergistically to resensitize the other isotypes, suggesting that increased tubulin protein, suggesting no increased by which Src may be promoting paclitaxel-induced microtubule decrease in Triton X-100–soluble monomeric tubulin and the paclitaxel-resistant ovarian cancer cells. This was shown by the stabilization in both paclitaxel-sensitive and paclitaxel-resistant ovarian cancer cells. In fact, we observed a decrease in βIII-tubulin protein in CaOV3TaxR cells in comparison with the paclitaxel-sensitive CaOV3 parental cell line and no change in ID8TaxR cells in comparison with ID8 cells. There were also no significant changes in βI-tubulin or βIV-tubulin protein, suggesting no increased βIII-tubulin as a ratio of the other isotypes, suggesting that increased βIII-tubulin protein is not a prerequisite for paclitaxel resistance.

SIRC inhibition seems to promote the ability of paclitaxel to stabilize microtubule dynamics in both paclitaxel-sensitive and paclitaxel-resistant ovarian cancer cells. This was shown by the decrease in Triton X-100–soluble monomeric tubulin and the increased Triton X-100–insoluble polymeric tubulin in response to the combination of Src inhibition and paclitaxel. The mechanism by which Src may be promoting paclitaxel-induced microtubule stabilization is not yet known but may involve lowering the critical intracellular concentration at which paclitaxel can suppress microtubule dynamics and promote tubulin bundling. Furthermore, there does not seem to be great β-tubulin isotype selectivity: Both βI-tubulin and βIII-tubulin incorporation into microtubules increased in paclitaxel-treated cells in which Src had been inhibited compared with control or paclitaxel alone–treated cells; βIV showed the least effect of Src inhibition. Immunofluorescence also revealed that the combination treatment of Src inhibition and paclitaxel resulted in multipolar spindle formation involving βI-tubulin and βIV-tubulin. βIII-Tubulin was never observed in the multipolar spindle of combination-treated paclitaxel-resistant ovarian cancer cells. It is not clear whether this is due to a lack of incorporation of βIII-tubulin into the multipolar spindle in paclitaxel-resistant cells or due to the relatively low signal, making identification of spindle difficult; βIII does seem to localize to normal spindle in control and paclitaxel-treated paclitaxel-resistant ovarian cancer cells. The formation of the multipolar spindle ultimately results in apoptosis as shown by the activation of caspase 3 (10).

In summary, the current study shows that Src tyrosine kinase inhibition restores the sensitivity to paclitaxel-resistant cells by an MDR-1–independent mechanism. Src and MDR-1 coinhibition acted synergistically to decrease the effective concentration at which paclitaxel can induce microtubule stabilization and cell death. The results indicate that Src tyrosine kinase, which is overexpressed and constitutively activated in a high proportion of ovarian cancers (24), may provide an effective target for chemo-therapeutic intervention in drug-resistant ovarian cancer.

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References


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