Targeting the High-Mobility Group Box 3 Protein Sensitizes Chemoresistant Ovarian Cancer Cells to Cisplatin

Anirban Mukherjee, Van Huynh, Kailee Gaines, Wade Alan Reh, and Karen M. Vasquez

Abstract

Chemotherapeutic regimens for ovarian cancer often include the use of DNA interstrand crosslink–inducing agents (e.g., platinum drugs) or DNA double-strand break–inducing agents. Unfortunately, the majority of patients fail to maintain a durable response to treatment, in part, due to drug resistance, contributing to a poor survival rate. In this study, we report that cisplatin sensitivity can be restored in cisplatin-resistant ovarian cancer cells by targeting the chromatin-associated high-mobility group box 3 (HMGB3) protein. HMGB proteins have been implicated in the pathogenesis and prognosis of ovarian cancer, and HMGB3 is often upregulated in cancer cells, making it a potential selective target for therapeutic intervention. Depletion of HMGB3 in cisplatin-sensitive and cisplatin-resistant cells resulted in transcriptional downregulation of the kinases ATR and CHK1, which attenuated the ATR/CHK1/p-CHK1 DNA damage signaling pathway. HMGB3 was associated with the promoter regions of ATR and CHK1, suggesting a new role for HMGB3 in transcriptional regulation. Furthermore, HMGB3 depletion significantly increased apoptosis in cisplatin-resistant A2780/CP70 cells after cisplatin treatment. Taken together, our results indicate that targeted depletion of HMGB3 attenuates cisplatin resistance in human ovarian cancer cells, increasing tumor cell sensitivity to platinum drugs.

Significance: This study shows that targeting HMGB3 is a potential therapeutic strategy to overcome chemoresistance in ovarian cancer.

Introduction

Ovarian cancer is the fifth most common cause of cancer-related deaths among women worldwide. In the United States alone, it is estimated that approximately 22,000 new cases of ovarian cancer will be diagnosed, leading to approximately 14,000 deaths in 2018 (1). Ovarian cancer is difficult to detect and once it has progressed to stage III and IV, the 5-year survival rate is dismal at only approximately 33% (2). Further contributing to the high mortality rate in the patients with ovarian cancer is the common development of resistance to cisplatin- or carboplatin-based chemotherapy (3), after which, patients have an average progression-free survival of 3–4 months and a median overall survival of 9–12 months (4). Unfortunately, fewer than 15% of these patients will respond to further treatment (reviewed in ref. 4).

The mechanisms underlying cisplatin resistance in ovarian cancer cells include, but are not limited to, increased repair of cisplatin-DNA interstrand crosslinks (ICL), increased DNA damage tolerance, and increased drug efflux (5, 6). The nucleotide excision repair (NER) mechanism and translesion DNA synthesis are involved in processing ICLs (7), and are thought to be more efficient in cells resistant to cisplatin chemotherapy (reviewed in ref. 8). Cisplatin-induced DNA damage activates the checkpoint kinases ATM and ATR. Such activation can lead to the phosphorylation of CHK2 at Thr68, CHK1 at Ser345, and both CHK1 and CHK2 can induce cell-cycle arrest and apoptosis by phosphorylating proapoptotic proteins (9).

We have previously demonstrated that the high-mobility group box 1 (HMGB1) protein binds with high affinity to ICLs and acts as an NER cofactor in human cells (10, 11). Other members of the HMGB family, HMGB2 and HMGB3, share sequence and structural similarities with HMGB1 and possess two box domains, boxes A and B; where box A binds DNA and box B bends DNA, and acidic C-terminal tails. When we depleted HMGB1, HMGB2, or HMGB3 separately in human osteosarcoma cells and then subjected them to psoralen and UVA irradiation (to induce ICL formation), depletion of each was found to be cytotoxic. HMGB3, unlike HMGB1 and HMGB2, is expressed at low levels in normal cells, but is often overexpressed (up to 20-fold) in cancer cells, making it a potential selective therapeutic target; thus, we focused this study on HMGB3 (12). Importantly, HMGB3 has been shown to be associated with disease prognosis in a wide variety of cancers (13).

In this study, we investigated the effects of HMGB3 depletion on cisplatin sensitivity in cisplatin-sensitive (A2780) or cisplatin-resistant (A2780/CP70) human ovarian cancer cells. We found that HMGB3 depletion sensitized cisplatin-resistant ovarian cancer cells to cisplatin. In addition, apoptosis was increased in the cisplatin-resistant, HMGB3-depleted cells following cisplatin treatment. Furthermore, we found that HMGB3 was associated with the ATR and CHK1 promoters contributing to their
expression levels. Our novel findings indicate that HMGB3 may serve as a novel target for combination therapy to attenuate cisplatin resistance in patients with ovarian cancer.

Materials and Methods

Cell culture and determination of cisplatin LD₅₀ values

Cells were purchased from ATCC where they perform short tandem repeat profiling for cell line authentication. Cells were cultured as described previously (11). Cells were grown to 80% confluency and were passaged at least three times after thawing before any experiments were performed and were cultured for a period of 6 months to perform all the experiments and repetitions. The A2780/CP70 cells were treated with 1 μmol/L cisplatin every third passage to maintain cisplatin resistance. Testing for Mycoplasma was not performed. LD₅₀ values were determined using MTZ assays (Promega). For MTZ assays, approximately 50,000 A2780 or A2780/CP70 cells were plated per well in a 96-well plate and were treated with 0, 5, 10, 15, 20, or 25 μmol/L cisplatin and cell survival was measured 72 hours post-incubation, as recommended by the manufacturer.

siRNA transfection, cisplatin treatment, and induction of psoralen ICLs

siRNA treatments and induction of psoralen ICLs were performed as described previously (10, 11). Cisplatin solutions were prepared by dissolving 1 mg of cisplatin in 1 mL of 1× PBS supplemented with 140 mmol/L NaCl to generate a 3.3 mmol/L stock, stored at 4°C in an amber tube for no longer than 30 days. To assess DNA damage checkpoint signaling as a function of HMGB3 depletion, A2780 and A2780/CP70 cells were plated in 60-mm dishes and were treated with either HMGB3 siRNA, nontargeted siRNA, or left untreated. The siRNA sequences used are shown in Supplementary Table S1. Subsequently, A2780 cells were treated with 2 μmol/L and A2780/CP70 cells were treated with 10 μmol/L cisplatin, corresponding to their LD₅₀ values. To assess the total protein levels, cells were collected at 24, 48, 72, and 96 hours postcisplatin treatment, and subjected to Western blot analyses.

Western blot analysis

Western blots were performed as described previously (11) using primary anti-HMGB3 rabbit polyclonal antibody, ATM and p-ATM (Ser 1981), secondary anti-β actin rabbit polyclonal antibody (Abcam Biotechnology Company), CHK2, p-CHK2 (Thr68), ATR, p-ATR (Ser428), and p-CHK1 (Ser317; Cell Signaling Technology), and CHK1 (Santa Cruz Biotechnology). Western blots were performed as described previously (11) using primary anti-HMGB3 rabbit polyclonal antibody, ATM and p-ATM (Ser 1981), secondary anti-β actin rabbit polyclonal antibody (Abcam Biotechnology Company), CHK2, p-CHK2 (Thr68), ATR, p-ATR (Ser428), and p-CHK1 (Ser317; Cell Signaling Technology), and CHK1 (Santa Cruz Biotechnology). Western blots were performed as described previously (11) using primary anti-HMGB3 rabbit polyclonal antibody, ATM and p-ATM (Ser 1981), secondary anti-β actin rabbit polyclonal antibody (Abcam Biotechnology Company), CHK2, p-CHK2 (Thr68), ATR, p-ATR (Ser428), and p-CHK1 (Ser317; Cell Signaling Technology), and CHK1 (Santa Cruz Biotechnology).

Clonogenic assay

A total of 4 × 10⁴ U2OS cells were plated with or without siRNA treatment. SmartPool siGENOME HMGB1, HMGB2, HMGB3 siRNA, or nontargeting siRNA (Thermo Fisher Scientific) were used at 20 nmol/L final concentrations for each transfection as described above. siRNA-transfected A2780/CP70 cells were treated with 2 μmol/L cisplatin 48 hours following the second siRNA treatment. Nontransfected A2780/CP70 and A2780 cells were seeded at 4 × 10⁵ cells in 60-mm dishes and treated with 2 μmol/L cisplatin as controls. All samples were incubated with cisplatin for 72 hours, then treated cells were reseeded in four replicates of 1,000 cells each in 60-mm dishes. Plating efficiency was calculated at approximately 60% for both cell lines. Untreated, nontransfected A2780/CP70 and A2780 cells were seeded in the same manner to provide untreated controls. Colonies were allowed to form for 15 days and were subsequently visualized by fixing the cells with 95% ethanol for 10 minutes and then staining with 0.05% crystal violet for 30 minutes.

FACS analysis

A total of 4 × 10⁵ A2780 and A2780/CP70 cells were plated with or without HMGB3 and nontargeted siRNA (20 nmol/L) and then were treated with 2 μmol/L cisplatin. Forty-eight hours after cisplatin treatment, cells were collected using Trypsin-Ethylenediaminetetraacetic acid, washed twice with chilled 1× PBS, and fixed with 70% ethanol for 2 hours at 4°C. Subsequently, cells were stained with 20 μg/mL propidium iodide (final concentration) in PBS with 0.5% Triton-X and 20 μg/mL RNase A (final concentration) for 1 hour at 37°C. Cells were sorted using a BD FACS ARIA II Cell Sorter (BD Biosciences) and DNA content was measured.

qRT-PCR

Total RNA was isolated using the TRizol Reagent (Thermo Fisher Scientific) as per the manufacturer’s recommendation. Two micrograms of purified RNA for each experimental sample was used for reverse transcription assays using the High-Capacity cDNA Reverse Transcription Kit (Thermo Fisher Scientific) in a 20-μL reaction volume following the manufacturer’s recommendation. cDNA (100 ng) was used for qPCR using iTaq Universal SYBR Green Supermix (Bio-Rad Laboratories) in 10-μL reaction volumes and samples were amplified using a ViiA 7 Real-Time PCR system (Thermo Fisher Scientific) using the machine default setup for amplification, and data were visualized and analyzed using the ViiA 7 software. The primer sequences used to amplify DNA are shown in Supplementary Table S2.

Chromatin immunoprecipitation assay

Chromatin immunoprecipitation assays were performed as described previously (11). In brief, 10⁶ A2780 and A2780/CP70 cells were plated. Twenty-four hours later, cells were fixed and chromatin preps were immunoprecipitated with ATR (Cell Signaling Technology) and CHK1 (Santa Cruz Biotechnology) antibodies using the SimpleChIP Enzymatic Chromatin IP Kit (Cell Signaling Technology). Samples were amplified using a ViiA 7 Real-Time PCR system (Thermo Fisher Scientific) using primers shown in the Supplementary Table S3. A 321-bp region was amplified with the ATR1 and CHK1 primers and a 285-bp product was amplified with the ATR2 primers (−147 to +158 from the transcription start site).

Statistical analysis

Statistical analyses were carried out using GraphPad Prism software. Tests performed to determine P values are indicated in the figure legends.

Analysis of The Cancer Genome Atlas for HMGB protein expression and gene alterations

Alterations in copy numbers, mutations, and expression levels of different HMGB genes were analyzed on the basis of the sequence data from The Cancer Genome Atlas (TCGA; ref. 14; PanCancer Atlas; TCGA provisional) using the cbioPortal (http://www.cbioportal.org; ref. 12). HMGB protein levels were analyzed using The Human Protein Atlas (15).
Results

In U2OS cells, we found an increased sensitivity to psoralen ICLs in the absence of the HMGB proteins (Fig. 1A; Supplementary Fig. S1) with HMGB3 depletion showing a similar effect on cell sensitivity compared with HMGB1 depletion. Importantly, analysis of the alterations in copy numbers, mutations, and expression levels from TCGA indicated up to 20-fold upregulation of HMGB3 expression in cancer cells (Supplementary Fig. S2A and S2B). HMGB1 is ubiquitously expressed at high levels compared with HMGB3 in normal cells, but the levels of HMGB1 and HMGB3 are very similar in cancer cells (Supplementary Fig. S2C and S2D). This overexpression of HMGB3 in cancer cells makes it a potential selective target for therapeutic intervention. Furthermore, we observed an increased gene alteration frequency of HMGB3 (more than 6%, predominantly in gene amplification events) in human serous ovarian cancer compared with HMGB1 (less than 2% gene alteration) and HMGB2 (slightly over 4%; Fig. 1B).

We confirmed that the cisplatin-resistant A2780/CP70 cells were approximately 10-fold more resistant to cisplatin (Supplementary Fig. S3), as published previously (16). Targeting HMGB3 using an siRNA-based approach consistently achieved approximately 90% reduction in protein levels (Fig. 1C). Subsequently, we treated the cells with cisplatin and measured colony formation. The A2780 cells treated with 2 μmol/L cisplatin showed nearly undetectable levels of colony formation relative to the untreated control cells, while A2780/CP70 cells treated with 2 μmol/L cisplatin showed high (~100%) clonogenic survival (Fig. 1D), as expected. Interestingly, when HMGB3 was depleted in the cisplatin-resistant A2780/CP70 cells, cisplatin treatment at a concentration (at 2 μmol/L) approximately 5-fold lower than that of the LD50 values, significantly reduced clonogenic survival by approximately 50% (Fig. 1D; Supplementary Fig. S3). These results indicated that depletion of HMGB3 substantially sensitized cisplatin-resistant A2780/CP70 cells to cisplatin treatment.

Figure 1.

HMGB3 depletion increases cisplatin sensitivity in cisplatin-resistant human ovarian cancer cells. A, Clonogenic survival of U2OS cells, treated with psoralen and 1.8 J/cm² UVA (365 nm) to induce ICLs, as a function of HMGB protein depletion. NTC, nontreated control; NSsi, nonspecific siRNA; HMGB1–3, specific siRNAs against each protein as listed. B, Alteration of the HMGB genes. Red, gene amplification; blue, deletions; green, point mutations. C, Schematic outline of the siRNA treatment and clonogenic survival assay along with siRNA-mediated depletion of HMGB3 in A2780/CP70 cells, evaluated by Western blot analysis. On average, approximately 90% HMGB3 depletion was detected from three independent experiments. KD, knockdown; NT, cells treated with nontargeting siRNA (Mock KD). D, Colony formation was evaluated using a clonogenic assay and visualized by fixing the cells with 95% alcohol and staining with 0.05% crystal violet. Various treatments are listed on the right side of the panel. The bar graph represents quantification of colony numbers from three independent experiments. Error bars, ± SD. The P values were determined via t test and P values of 0.05 or lower were considered significant. ****, P < 0.00005. CP, cisplatin.
Consistent with the clonogenic survival assays (Fig. 1D), HMGB3-depleted, cisplatin-treated A2780 cells showed an approximately 6% increase in the sub-G1 population (Fig. 2A) while the A2780/CP70 cells showed an approximately 24% increase in the sub-G1 cell population compared with the control cells within 24 hours of treatment (Fig. 2B), suggesting an increase in the apoptotic cell population. Average sub-G1 values for non-targeted siRNA and HMGB3-siRNA–treated A2780 cells following cisplatin treatment were 39.6% and 33.4%, respectively (Fig. 2A). The nontargeted siRNA-treated cells showed an increase in the sub-G1 population (average sub-G1 20.2% compared with 6.7%; Fig. 2B) but it was less than that in the HMGB3-siRNA-treated cells and could be due to the toxic nature of the siRNA transfection method itself.

To examine a potential role of HMGB3 depletion in increased chemosensitivity of the resistant A2780/CP70 cells, we evaluated DNA damage responses following cisplatin treatment by measuring the levels of the ATM, phospho-ATM, ATR, phospho-ATR, CHK2, phospho-CHK2, CHK1, and phospho-CHK1 checkpoint kinases at different time points in both the A2780 and A2780/CP70 cells. Western blot analysis of whole-cell lysates (Fig. 3A and B) and subsequent densitometric quantification of the protein levels revealed that the ATR, CHK1, and p-CHK1 kinase levels were significantly reduced (by ≈50% at 24 hours and >50% at 48, 72, and 96 hours) up to 96 hours after cisplatin treatment as a function of HMGB3 depletion in both cell lines (Fig. 3C and D). Our results indicated that HMGB3 depletion significantly lowered the distribution of the averages of ATR/p-ATR (P < 0.0001) and CHK1/pCHK1 (P < 0.0001) in both the cisplatin-sensitive and cisplatin-resistant cells when compared with the nontargeting siRNA-treated groups, suggesting a disruption in DNA damage signaling as a probable cause of increased cell death (as shown in Fig. 1D). Interestingly, we observed a significantly lower distribution of the averages of the p-ATM levels in both cell lines.
HMGB3 modulation of cisplatin sensitivity in ovarian cancer cells. 

Figure 3.

Analysis of DNA damage checkpoint signaling kinases following treatment with cisplatin as a function of HMGB3 depletion. A, Untreated (NTC), nontargeting siRNA (NT siRNA), or HMGB3 siRNA-treated A2780 ovarian cancer cells were exposed to cisplatin (2 μmol/L, the LD50 concentration) and cells were collected 24, 48, 72, and 96 hours after treatment. Twenty to forty micrograms of total protein was loaded per lane and resolved by SDS-PAGE, probed with indicated antibodies, and visualized via Western blot analysis. B, The cisplatin-resistant A2780/CP70 cells were treated as described above with siRNA and then with 10 μmol/L cisplatin (the LD50 concentration) to analyze the levels of the DNA damage response proteins as above. All experiments were repeated at least three times. Representative blots are shown. C and D, Densitometric quantification of checkpoint kinases from experiments represented in Fig. 2A and B. All samples were normalized against the loading control, β-actin. Furthermore, the HMGB3 siRNA-treated samples (orange bars) were normalized against nontargeting siRNA (NT siRNA)-treated samples (blue bars) to determine the effects of HMGB3 depletion on DNA damage responses to cisplatin treatment over time (as listed in the figure). The solid bars represent the average amount of protein detected from at least three experiments, and the bars with the striped pattern represent the phosphorylated forms of the proteins. ATR and CHK1/pCHK1 protein levels were consistently lower in the cisplatin-treated A2780 and A2780/CP70 cells when HMGB3 was depleted. Error bars, ± SD. The differences in the distributions of the samples in the NT siRNA-treated control groups and HMGB3 siRNA-treated groups were determined using the Bonferroni Mann–Whitney U test method and P < 0.05 was considered significant. *, P < 0.05. The distributions of the averages of the ATR/p-ATR and CHK1/p-CHK1 samples were significantly lower (P < 0.0001) in the HMGB3 siRNA-treated groups compared with the NT siRNA-treated groups in both the cell lines. The distributions of the averages in the p-ATM samples were significantly different in A2780 (**, P < 0.005) and in A2780/CP70 cells (P < 0.0048) in the HMGB3 siRNA-treated samples compared with NT siRNA-treated samples. No such significant difference was observed in the p-CHK2 samples.

(P = 0.005 for A2780 cells and 0.0048 for the A2780/CP70 cells) but not of the average p-CHK2 levels in the HMGB3 siRNA-treated samples, indicating no clear relationship between HMGB3 depletion and the ATM/p-ATM and CHK2/p-CHK2 damage signaling pathway. These data indicated that HMGB3 depletion led to the attenuation of the ATR-CHK1-p-CHK1 DNA damage signaling pathway after cisplatin treatment.

Cisplatin treatment has been shown to modulate gene expression profiles in ovarian cancer cells (17). We observed a decrease in the HMGB3 expression levels over time in A2780 cells following cisplatin treatment and was significantly lower at 96 hours in A2780 cells, but not in the chemoresistant A2780/CP70 cells (Fig. 3A and Fig. 4A). Subsequently, we measured the mRNA levels of the ATR and CHK1 kinases as a function of HMGB3 depletion and determined that the total mRNA levels were significantly lower in both A2780 and A2780/CP70 cells (Fig. 4B). These results indicated that ATR and CHK1 expression levels were, to an extent, associated with the HMGB3 levels in the ovarian cancer cells. Furthermore, via chromatin immunoprecipitation assays, we found that HMGB3 was associated with the promoter/enhancer regions of ATR and CHK1 in the human genome, while the association of HMGB3 with the CHK1 promoter appeared to be stronger than that of the ATR promoter in this assay (Fig. 4C). Consistent with its role in modulating gene expression, we observed significant reduction of luciferase expression in both ovarian cancer cell types when HMGB3 was depleted (Supplementary Fig. S4), suggesting that HMGB3 may be involved in modulating transcription in the ovarian cancer cells.

Discussion

The HMGB proteins are architectural proteins that, among other things, regulate chromatin structure, facilitate transcriptional regulation, bind preferentially to alternative DNA structures or damaged DNA, and play a role in multiple DNA repair pathways. The data presented here demonstrate a role of HMGB3 in sensitizing cisplatin-resistant ovarian cancer cells to cisplatin treatment, possibly via the transcriptional repression and deregulation of the ATR-CHK1 damage signaling pathway.

The occurrence of cisplatin resistance is currently a therapeutic limitation in the course of ovarian cancer treatment, as well as in the treatment of other cancers. To counter the increased efflux of drugs in these resistant cells (5, 18), multiple approaches have been explored. For example, small-molecule chemosensitizers such as colchicine, genistein, and rapamycin were shown to increase the intracellular accumulation of cisplatin in ovarian cancer cells in vitro, resulting in reduced cell survival following cisplatin treatment (19). Other small molecules have been shown to improve responses to cisplatin by reducing the expression of the multidrug resistance associated protein 2, ultimately increasing intracellular cisplatin concentrations. Alternatively, studies have shown that inhibition of various signaling pathways, including the IGF signaling pathway and colony-stimulating-factor 1
receptor, may improve responses to cisplatin treatment in resistant tumor cells (20, 21!1). Upregulation of proapoptotic proteins (22) and/or the inhibition of the expression of PARP-1, a protein involved in DNA repair, have also shown potential for overcoming cisplatin resistance (23).

Targeting the HMGB proteins has shown some promise in cancer therapy, although targeting HMGB1 has been a matter of debate due to the conflict between its intracellular DNA-associated functions and extracellular cytokine functions (24). Nevertheless, HMGB1 has been shown to be a promising therapeutic target for prostate cancer (25). siRNA-mediated depletion of HMGB2 has been shown to increase chemo- and radiosensitivity of head and neck squamous cell carcinomas (26), breast cancer cells (27), and colorectal cancer cells (28). Similarly, HMGB3 depletion has been shown to lower the proliferative potential of colorectal cancer cells (29).

Our novel findings indicating the upregulation of HMGB3 in cancer cells, and its role in transcriptional repression of the DNA damage signaling kinases ATR and CHK1, suggest that HMGB3 may represent a target in ovarian cancer for therapeutic intervention to overcome cisplatin resistance (23).

Figure 4. HMGB3 positively influences ATR and CHK1 transcription. A, Change in HMGB3 expression in A2780 and A2780/CP70 cells as a function of cisplatin treatment. B, Reduced ATR and CHK1 total mRNA levels in A2780 and CP70 cells as a function of HMGB3 depletion. Error bars, ± SD from a minimum of three experiments. *P < 0.05, **P < 0.005, determined by the paired t test. C, Chromatin immunoprecipitation assay showing the association of HMGB3 with the ATR promoters, ATR1 and ATR2, and the CHK1 promoter expressed as a percentage of input. Control indicates a region 2.5-kb upstream of the ATR1 promoter and RPL30 indicates the amplification of ribosomal protein L30 exon 3 as a negative control. IgG, immunoglobulin G; H3, histone 3; HMGB3, high-mobility group box 3 IP. The values represented are the averages of two experiments.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: A. Mukherjee, W.A. Reh, K.M. Vasquez
Development of methodology: A. Mukherjee, W.A. Reh, K.M. Vasquez
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): W.A. Reh
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A. Mukherjee, K. Gaines, W.A. Reh, K.M. Vasquez
Writing, review, and/or revision of the manuscript: A. Mukherjee, V. Huynh, K. Gaines, K.M. Vasquez
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A. Mukherjee, V. Huynh, K.M. Vasquez
Study supervision: A. Mukherjee, K.M. Vasquez

Acknowledgments
We would like to thank the DPRI core facility for assistance with the FACS analysis and would like to thank the Vasquez lab members for helpful discussions. This work was supported by NIH/NCI grants (CA193124 and CA093729; to K.M. Vasquez).

Received February 12, 2019; revised April 26, 2019; accepted May 1, 2019; published first May 6, 2019.

References
2. Scholz HS, Tasdemir H, Hunlich T, Turnwald W, Both A, Egger H. Multivisceral cytoreductive surgery in FIGO stages IIIIC and IV

HMGB3 Modulates Cisplatin Sensitivity
Targeting the High-Mobility Group Box 3 Protein Sensitizes Chemoresistant Ovarian Cancer Cells to Cisplatin

Anirban Mukherjee, Van Huynh, Kailee Gaines, et al.


Updated version
Access the most recent version of this article at:
doi:10.1158/0008-5472.CAN-19-0542

Supplementary Material
Access the most recent supplemental material at:
http://cancerres.aacrjournals.org/content/suppl/2019/05/04/0008-5472.CAN-19-0542.DC1

Cited articles
This article cites 29 articles, 8 of which you can access for free at:
http://cancerres.aacrjournals.org/content/79/13/3185.full#ref-list-1

Citing articles
This article has been cited by 1 HighWire-hosted articles. Access the articles at:
http://cancerres.aacrjournals.org/content/79/13/3185.full#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, use this link
http://cancerres.aacrjournals.org/content/79/13/3185.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.