Regulation of HSulf-1 Expression by Variant Hepatic Nuclear Factor 1 in Ovarian Cancer

Peng Liu,1 Ashwani Kurhana,1 Ramandeep Rattan,1 Xiaoping He,1 Steve Kalloger,3 Sean Dowdy,1 Blake Gilks,1 and Viji Shridhar1

Departments of 1Experimental Pathology and 2Obstetrics and Gynecology, Mayo Clinic College of Medicine, Rochester, Minnesota and 3Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, British Columbia, Canada

Abstract

We recently identified HSulf-1 as a down-regulated gene in ovarian carcinomas. Our previous analysis indicated that HSulf-1 inactivation in ovarian cancers is partly mediated by loss of heterozygosity and epigenetic silencing. Here, we show that variant hepatic nuclear factor 1 (vHNF1), encoded by transcription factor 2 gene (TCF2, HNF1β), negatively regulates HSulf-1 expression in ovarian cancer. Immunoblot assay revealed that vHNF1 is highly expressed in HSulf-1–deficient OV207, SKOV3, and TOV-21G cell lines but not in HSulf-1–expressing OSE, OV167, and OV202 cells. By short hairpin RNA–mediated down-regulation of vHNF1 in TOV-21G cells and transient enhanced vHNF1 expression in OV202 cells, we showed that vHNF1 suppresses HSulf-1 expression in ovarian cancer cell lines. Reporter assay and chromatin immunoprecipitation experiments showed that vHNF1 is specifically recruited to HSulf-1 promoter at two different vHNF1-responsive elements in OV207 and TOV-21G cells. Additionally, down-regulation of vHNF1 expression in OV207 and TOV-21G cells increased cisplatin– or paclitaxel-mediated cytotoxicity compared with xenografts of nude mice bearing TOV-21G cell xenografts with stably down-regulated vHNF1. Moreover, nude mice bearing TOV-21G cell xenografts with stably down-regulated vHNF1 were more sensitive to cisplatin- or paclitaxel-induced cytotoxicity compared with xenografts of TOV-21G clonal lines with nontargeted control short hairpin RNA. Finally, immunohistochemical analysis of 501 ovarian tumors including 140 clear-cell tumors on tissue microarrays showed that vHNF1 inversely correlates to HSulf-1 expression. Collectively, these results indicate that vHNF1 acts as a repressor of HSulf-1 expression and might be a molecular target for ovarian cancer therapy.

Introduction

Our previous studies have shown that HSulf-1, an extracellular sulfatase catalyzing the 6-O desulfation of heparan sulfate glycosaminoglycans, is down-regulated in the majority (75%) of tumor tissues harvested from ovarian cancer patients and is undetectable in clear-cell carcinoma of the ovary, a particularly aggressive and chemoresistant subtype (1). Loss of HSulf-1 expression augments both autocrine and paracrine proliferation signaling through various epidermal growth factor–like growth factor family ligands, such as epidermal growth factor, amphiregulin, and heparin-binding epidermal growth factor–like growth factor, resulting in an increase tumor cell growth and resistance to drug-induced apoptosis (1, 2). In addition, reexpression of HSulf-1 inhibits both tumor growth and tumor angiogenesis in vivo (3).

Variant hepatic nuclear factor 1 (vHNF1; also called HNF1β or TCF2) protein were initially identified based on its interaction with a sequence essential for liver-specific transcription of several genes postulated to determine the hepatic phenotype (4). Subsequent studies have shown that there is a high level of vHNF1 expression in pancreas, kidney, stomach, lung tissue, and hepatocellular carcinoma (5). Mutations of the human vHNF1 gene are associated with maturity onset diabetes of the young type 5 (MODY5) and renal carcinomas (6).

Despite the fact that it is highly curable if diagnosed early, cancer of the ovaries causes more mortality in American women each year than all other gynecologic malignancies combined (7). Clear-cell ovarian cancer represents 2% to 15% of all epithelial ovarian malignancies and has several clinical and histologic characteristics distinguishing it from other types of ovarian cancers (8). For instance, all of the epithelial ovarian cancers, clear-cell carcinoma has the worst prognosis partially because of its low response to standard platinum-based chemotherapy (9–12). Several investigations have indicated that vHNF1 is overexpressed in clear-cell carcinoma and can be an excellent molecular marker of this disease (13, 14). Other studies have shown that hypomethylation of vHNF1 CpG island participates in the up-regulation of vHNF1 in clear-cell carcinoma (15). Furthermore, down-regulation of vHNF1 expression by RNA interference induced apoptotic cell death in ovarian clear-cell carcinoma cell lines (8). As indicated, our studies of HSulf-1 expression have revealed that there is a much higher frequency of loss of HSulf-1 expression in clear-cell tumors (100%) of the ovary compared with serous histologic subtype (70%; ref. 1). Therefore, we hypothesized that vHNF1 may negatively regulate HSulf-1 expression in ovarian carcinomas.

In the present study, we report on the expression profile of vHNF1 in ovarian cell lines and primary ovarian cancers by immunoblot and tumor tissue microarray analysis. Additionally, chromatin immunoprecipitation and luciferase reporter assays show that vHNF1 is specifically recruited to HSulf-1 promoter at vHNF1-responsive elements (vHRE) in vivo and can markedly reduce HSulf-1 promoter activity in vitro. Using lentiviral-mediated short hairpin RNA (shRNA) technology, we also investigated the effect of down-regulation of vHNF1 on HSulf-1 expression and sensitivity to chemotherapy of ovarian cancer cells both in vitro and in vivo.
Materials and Methods

Cell culture. TOV-21G, SKOV3, OVCAR3, and OVCAR5 cells were purchased from the American Type Culture Collection. OV167, OV202, and OSE cell lines were established as described previously (16, 17). A2780 cell line was obtained on a MTA from Dr. Thomas Hamilton (Fox Chase Cancer Center). All cell lines were grown as reported previously (16, 17).

Protein extracts and Western blot. Protein extraction and Western blot analysis were done as described previously (2). The antibodies used for immunoblotting were as follows: HSulf-1 (Abcam), vHNF1 (Santa Cruz Biotechnology), and HNF1α (Santa Cruz Biotechnology).

shRNAs. The shRNAs used in this study are listed in the Supplementary Experiment Procedures and Supplementary Table S1.

Plasmid constructions. The construction of all plasmids used in this study is described in Supplementary Experiment Procedures. The sequences of primers used for the amplification of constructs are listed in Supplementary Table S1.

Luciferase reporter assays. Reporter assay was done as described previously (18). See also Supplementary Experiment Procedures.

Chromatin immunoprecipitation assay. Chromatin immunoprecipitation assays were done as described (16). See also Supplementary Experiment Procedures.

Results

Expression analysis of HSulf-1 and vHNF1 in ovarian cancer cell lines. HSulf-1 and vHNF1 expression were evaluated in seven ovarian cancer cell lines and normal ovarian epithelial cells (OSE) by Western blot. As shown in Fig. 1A, OSE, OV167, and OV202 cells express HSulf-1, whereas A2780, OV207, TOV-21G, SKOV3, and OVCAR5 have undetectable or very low levels of HSulf-1 expression. However, vHNF1 is highly expressed in HSulf-1–deficient OV207, SKOV3, and TOV-21G cell lines and weakly in A2780 and OVCAR5 cells but not in HSulf-1–expressing OSE, OV167, and OV202 cells.

Forced expression of vHNF1 in OV202 cells down-regulated HSulf-1 expression. Lack of vHNF1 expression in HSulf-1–expressing cell lines led us to speculate that vHNF1 could act as a repressor of HSulf-1 expression. To test this hypothesis, we transiently transfected vHNF1 expression construct into OV202 cells. Forty-eight hours following transfection, HSulf-1 expression levels were determined by immunoblot and real-time quantitative reverse transcription-PCR. As shown in Fig. 1B, forced expression of vHNF1 in OV202 cells reduced HSulf-1 expression at both protein and mRNA levels.

shRNA-mediated down-regulation of vHNF1 up-regulated HSulf-1 expression. To test if down-regulation of endogenous vHNF1 may up-regulate HSulf-1 expression, vHNF1 was silenced using lentiviral-mediated shRNAs in OV202 and TOV-21G cells as described in Materials and Methods. The nontarget shRNAs served as controls. As shown in Fig. 1C, our immunoblot analysis showed that shRNAs targeting two different regions of vHNF1 open reading frame markedly decreased the expression of vHNF1 compared with the control shRNA in both cell lines. Attenuation of vHNF1 expression resulted in an increase of HSulf-1 protein expression, which was more pronounced in TOV-21G cells compared with OV207 cells. Down-regulation of vHNF1 also led to increased HSulf-1 expression at mRNA level in both cell lines.

Overexpression of vHNF1 decreases HSulf-1 promoter activity via vHREs. Based on the regulatory effect of HSulf-1 expression by vHNF1, we analyzed the databases TRANFAC and Transcription Element Search System for consensus binding site for vHNF1 transcription factor upstream of transcription initiation site on HSulf-1 promoter. Sequence analysis of HSulf-1 promoter using Transcription Element Search System revealed the presence of three vHREs (5′-ATTAC-3′) upstream of the transcription initiation site. The diagrammatic representation of these elements in HSulf-1 promoter is shown in Fig. 2A. The 1 kb promoter sequence was cloned into a pGL3-Basic luciferase reporter plasmid. Dual-luciferase assays were done on cell extracts from OV202 cells cotransfected with luciferase reporter plasmid and either pvHNF1

4 http://www.cbil.upenn.edu/cgi-bin/tess/tess
or pcDNA3.1 empty vector. As shown in Fig. 2B, overexpression of vHNF1 significantly reduced HSulf-1 promoter activity compared with controls. Figure 1B (left, lane 2) shows the level of HSulf-1 on transient transfection of vHNF1 in OV202 cells.

To determine which of the three vHRE binding sites are required for the inhibitory effect of vHNF1 on HSulf-1 promoter activity, TT→GG (for first and second vHRE sites) and TA→GC (for third vHRE in the opposite orientation) mutations that destroy the vHNF1 binding were introduced into the vHNF1 binding sites, respectively. Mutation of either vHRE2 or vHRE3 abolished transcriptional repression of HSulf-1 by vHNF1. However, there was no change in vHNF1 promoter activity when vHRE1 was mutated (Fig. 2B). Mutations of both vHRE2 and vHRE3 in the same construct also rescued HSulf-1 promoter activity, although the effects were not additive. Collectively, these results indicate that both vHRE2 (close to the transcriptional initiation site) and vHRE3, distal to vHRE2, could be functionally relevant to regulate HSulf-1 expression.

**vHNF1 is specifically recruited to HSulf-1 promoter.** To determine whether vHNF1 is recruited to HSulf-1 promoter, chromatin immunoprecipitation assays were done in OV207 and TOV-21G cells. For each cell line, DNA/protein complexes were immunoprecipitated with anti-vHNF1 antibody and the purified DNA was amplified with primers flanking vHRE1 and 3 sites in one reaction and with primers (Supplementary Table S1) flanking vHRE2 in another. The location of the three potential vHNF1 binding sites in HSulf-1 promoter and the primers used for chromatin immunoprecipitation assay are shown in Fig. 2A.
shown in Fig. 2C and D, vHNF1 is recruited to two different regions within the HSulf-1 promoter in both TOV-21G and OV207 cells but not in OV202 cells, which do not express vHNF1 (data not shown). The first region spans vHRE1 and vHRE3, which are very close to each other (Fig. 2A), whereas the second region contains vHRE2. We confirmed that the recruitment was specific because there was undetectable or very little amplification of IgG controls (Fig. 2C and D, lanes 1 and 4).

Down-regulation of vHNF1 sensitizes ovarian cancer cells to cisplatin- or paclitaxel-mediated cytotoxicity. Our previous data showed that HSulf-1 expression confers chemosensitivity to multiple drugs in ovarian cancer (1). Therefore, we tested the effect of down-regulation of vHNF1 on HSulf-1 expression and the sensitivity of cancer cells to cisplatin and paclitaxel. We down-regulated vHNF1 expression in the two ovarian clear-cell-derived cell lines, OV207 and TOV-21G, using lentiviral shRNAs against vHNF1 and generated batch clones. vHNF1 down-regulation was confirmed by Western blot as shown in Fig. 1C. Both vHNF1 down-regulated batch clone and nontarget control cells were treated with increasing concentrations of cisplatin or paclitaxel for 24 h and were then incubated in fresh medium for additional 3 days. As shown in Fig. 3A and B, shRNA mediated down-regulation of vHNF1 in both OV207 and TOV-21G cells resulted in increased sensitivity to both cisplatin and paclitaxel as determined by MTT reduction assay compared with cells transduced with nontarget shRNA. To test whether cisplatin- or paclitaxel-induced antiproliferative effects translated into less clonogenic survival, we tested the clonogenic survival of OV207 and TOV-21G batch clonal lines. Both control and vHNF1 down-regulated batch clones were treated with various concentrations of cisplatin or paclitaxel for 24 h, allowed to grow for additional 10 days in drug-free medium, and then counted for surviving colonies after Coomassie staining. Consistent with the previous results, down-regulation of vHNF1 attenuated clonogenic survival of cells transduced with shRNAs targeting vHNF1 compared with the control cells (Fig. 3C and D). However, shRNAs targeting vHNF1 have no effect on both HSulf-1 protein expression and cisplatin-induced cytotoxicity in vHNF1-deficient OV202 (Supplementary Fig. S1). These results suggest that down-regulation of vHNF1 promotes chemotheraphy-induced cytotoxicity in ovarian cancer cell lines.

Specific contribution of HSulf-1 in conferring cisplatin-induced cytotoxicity in TOV-21G cells following vHNF1 down-regulation. Our results indicate that down-regulation of vHNF1 in OV207 and TOV-21G cells results in the up-regulation of HSulf-1 expression. Additional studies indicate that, under these conditions, the cells become sensitive to cisplatin-induced cytotoxicity. However, down-regulation of vHNF1 could result in changes of several vHNF1 target gene expression (19). To determine the specific contribution of HSulf-1 in cisplatin-induced cytotoxicity, we transiently down-regulated HSulf-1 expression with siRNA in TOV-21G cells with down-regulated vHNF1 expression. Down-regulation of both vHNF1 and HSulf-1 was determined by immunoblot analysis (Fig. 4, inset). As seen in Fig. 4, there is loss of both vHNF1 and HSulf-1 expression in cells transfected with

![Figure 2. Involvement of vHNF1 in suppression of HSulf-1 promoter activity. A, schematic representation of potential vHNF1 binding sites in HSulf-1 promoter and the location of the primers used for chromatin immunoprecipitation assay. B, suppression of HSulf-1 transcription by vHNF1 requires functional vHREs. OV202 cells were cotransfected with either wild-type HSulf-1 luciferase reporter construct or plasmids containing mutations in the putative vHNF1 binding sites (slashed oval, white ones indicate vHREs in the opposite orientation) as well as pvHNF1 or pcDNA3.1 empty vector. The relative luciferase activity is presented as a percentage of the luciferase activity of the cells transfected with wild-type promoter construct and pcDNA3.1 empty vector. Mean ± SD of triplicate samples. Results indicate that both vHRE2 and vHRE3, but not vHRE1, could be functionally relevant to regulate HSulf-1 expression. C and D, vHNF1 is recruited to specific sites within HSulf-1 promoter. Chromatin immunoprecipitation assay was done to show in vivo binding of vHNF1 on HSulf-1 promoter. Anti-vHNF1 antibody or goat IgG was used to precipitate sonicated chromatin from TOV-21G (C) and OV207 (D). Input control DNA was diluted 5-fold before PCR amplification.](cancerres.aacrjournals.org)
HSulf-1 siRNA (Fig. 4, inset, lane 3), whereas the scrambled siRNA-transduced controls express HSulf-1 but not vHNF1 (Fig. 4, inset, lane 2). We used shvHNF1-2 batch clones in this experiment, as it showed higher efficacy of vHNF1 knockdown than the other transfectant shvHNF1-1 in TOV-21G cells (Fig. 1C). Two days following HSulf-1 siRNA transfection, the cells were treated with increasing concentrations of cisplatin for 24 h and tested by MTT reduction assay. Suppression of vHNF1 expression sensitized cancer cells to drug-induced antiproliferative effects in both cell lines. C and D, OV207 and TOV-21G batch clonal cells expressing shRNAs targeting vHNF1 or nontargeting shRNA were treated with the indicated concentrations of cisplatin or paclitaxel for 24 h, washed, and allowed to form colonies. Stable inhibition of vHNF1 led to decreased clonogenic survival compared with the controls. Mean ± SD of triplicates samples. *, P < 0.05; **, P < 0.01.

Figure 3. shRNAs targeting vHNF1 promotes cisplatin/paclitaxel toxicity. A and B, OV207 and TOV-21G batch clonal cells stably expressing shRNAs to vHNF1 were exposed to varying concentrations of cisplatin or paclitaxel for 24 h and tested by MTT reduction assay. Suppression of vHNF1 expression sensitized cancer cells to drug-induced antiproliferative effects in both cell lines. C and D, OV207 and TOV-21G batch clonal cells expressing shRNAs targeting vHNF1 or nontargeting shRNA were treated with the indicated concentrations of cisplatin or paclitaxel for 24 h, washed, and allowed to form colonies. Stable inhibition of vHNF1 led to decreased clonogenic survival compared with the controls. Mean ± SD of triplicates samples. *, P < 0.05; **, P < 0.01.

vHNF1 inhibition enhances the antiproliferative activity of cisplatin or paclitaxel in vivo. Xenografts of TOV-21G transfectants stably expressing control shRNA or shvHNF1-1/2 were generated and treated as described in Materials and Methods. Measurements of tumors volume are graphically displayed in Fig. 5A and B. Down-regulation of vHNF1 significantly increased the in vivo sensitivity of TOV-21G cells to both drugs used in this study, which is consistent with our in vitro experiments. Sustained down-regulation of vHNF1 and HSulf-1 up-regulation in the xenografts are confirmed by immunoblot (Fig. 5C and D). This is the first demonstration that vHNF1 gene silencing can induce HSulf-1 expression and potentiate the antiproliferative effect of cisplatin and/or paclitaxel in vivo.
**vHNF1 inversely correlates to HSulf-1 expression in primary ovarian cancers.** To evaluate the potential association between vHNF1 and HSulf-1 expression and clinicopathologic parameters in ovarian cancer, a tissue microarray containing a total of 501 primary ovarian tumor samples was analyzed (Fig. 6). vHNF1 immunostaining was predominantly found in the nucleus; 20.6% (103 of 501) of ovarian tumors had positive staining of vHNF1, of which 63.1% (65 of 103) of cases showed negative staining for HSulf-1. Conversely, higher level of HSulf-1 was detected in 61.8% (246 of 398) of samples that were negative for vHNF1 staining. Thus, vHNF1 was inversely correlated with HSulf-1 expression level ($P < 0.0001$). There was no relationship between vHNF1 and disease stage and grade ($P > 0.05$). Additionally, serous tumors with moderate to high levels of HSulf-1 (127 of 186, 68.3%) showed a trend toward improved survival as assessed by Kaplan-Meier survival analysis and log-rank test ($P = 0.0465$; Supplementary Fig. S2). However, we did not observe this trend in either endometrioid or clear-cell tumors potentially due to the limited numbers of HSulf-1–positive tumors with these two subtypes ($P > 0.05$; data not shown).

**Discussion**

We have previously shown that mRNA encoding HSulf-1 is down-regulated in ovarian cancer (1). HSulf-1 down-regulation modulates heparin-binding growth factor signaling and epigenetic modifications contribute in part to its down-regulation in human cancers (16, 20, 21). We have also reported that HSulf-1 is a key regulator of vascular endothelial growth factor-mediated proliferation and that loss of HSulf-1 leads to increased tumorigenesis and angiogenesis in vivo (3). In particular, patients with ovarian cancers expressing higher levels of HSulf-1 showed a 94.4% response rate (17 of 18) compared with a 58% (7 of 12) response rate among those with weak or moderate levels of HSulf-1 expression (16). Accordingly, HSulf-1 down-regulation appears to represent a mechanism by which ovarian cancer cells enhance growth factor signaling and diminish apoptosis.

Clear-cell ovarian cancers represents 2% to 15% of all epithelial ovarian malignancies (22) and is associated with a poorer outcome compared with serous carcinoma (12, 23). Several investigations indicated that vHNF1 could be an excellent marker and a possible molecular target for therapy for ovarian clear-cell carcinoma (8, 24, 25). Recent studies by Köbel and colleagues (14) showed that vHNF1 showed the highest sensitivity (82.5%) and specificity...
(95.2%) for clear-cell carcinoma. Based on our previous data showing that HSulf-1 expression seems to be down-regulated or lost in a much higher proportion of clear-cell tumors of the ovary compared with other histologic subtypes (1), we surmised that expression of HSulf-1 could be regulated by vHNF1. Consistent with this hypothesis, sequence analysis showed the presence of three vHREs upstream of the transcriptional start site of HSulf-1 promoter.

Immunoblot analysis of vHNF1 expression seemed to indicate that loss of HSulf-1 could be associated with expression of vHNF1. Of interest to this study is the observation that the HSulf-1–expressing cell lines (OSE, OV167, and OV202) had complete loss of vHNF1 expression, suggesting that vHNF1 could be a repressor of HSulf-1 expression. Contrary to the report by other investigators (8, 13), we found that non–clear-cell-derived cell lines, such as SKOV3 cells, also expressed significant amounts of vHNF1 and also lower levels of HSulf-1 in OVCA5 and A2780 cells in addition to robust expression of vHNF1 in cell lines derived from clear-cell tumors, OV207 and TOV-21G (Fig. 1A). However, Tomassetti and colleagues (26) and Terasawa and colleagues (27) reported that other non–clear-cell-derived cell lines such as IGROV1, SKOV3, and OVCAR3 cell lines express vHNF1.

Consistent with these observations, several findings from this study indicate a regulatory role for vHNF1 in the control of HSulf-1 transcription. By shRNA-mediated down-regulation of vHNF1 in TOV-21G cells and transient enhanced vHNF1 expression in OV202 cells, we showed that vHNF1 suppresses HSulf-1 expression in ovarian cancer cell lines. We have also shown a decrease in HSulf-1 transcriptional activity in luciferase reporter assays following overexpression of vHNF1 protein in OV202 cells and that it is mediated through two different vHREs (vHRE2 and vHRE3) in HSulf-1 promoter, which was further confirmed by chromatin immunoprecipitation assays. However, we did not see a significantly more transcriptional activation of HSulf-1 on simultaneous mutation of both sites, implicating that other cofactors could be involved in regulating the activity of vHNF1 as observed for HNF-1α, where a dimerization cofactor Dcoh selectively stabilized HNF-1α dimers and enhanced its transcriptional activity in a tissue-specific manner (28).

Other studies indicate that members of the HNF family, for example, a closely related member of the family of HNF proteins, HNF1α, mediate transcriptional activation (29). HNF1α is a homeodomain-containing protein that acts as a transcriptional activator to regulate a large group of genes and associated with development, metabolism, and cancer. The homeodomain and dimerization domain, but not the activation domain, are highly conserved between HNF1α and vHNF1 (HNF1β). Because vHNF1 lacks transcription activation domains, it is not surprising to note that it has no or lower transactivation potency than that of HNF1α (29). In addition, vHNF1 has been associated with repression of a subset of hepatocyte-specific genes (30). It seems that HNF1α and vHNF1 may regulate a different set of genes in vivo, although they do not distinguish between the DNA-binding sites in vitro (29). We also explored the potential regulatory role of HNF1α in HSulf-1 expression and found that overexpression of HNF1α could change neither protein/mRNA level nor promoter activity of HSulf-1 in ovarian cancer cell lines. Moreover, chromatin immunoprecipitation assay showed that HNF1α does not bind to HSulf-1 promoter region in vivo (data not shown). These results indicate that the inhibitory effect of vHNF1 on HSulf-1 expression may be independent of HNF1α.

Additional studies indicate that stable down-regulation of vHNF1 sensitizes OV207 and TOV-21G cells to cisplatin- or paclitaxel-induced cytotoxicity both in vitro and in vivo (Figs. 3 and 5). As shown in Fig. 5, mouse bearing stably depleted vHNF1 TOV-21G xenografts were sensitive to both cisplatin and paclitaxel treatment compared with vHNF1-proficient TOV-21G xenografts. Consistent with this, we found elevated levels of HSulf-1 in the tumor xenografts (Fig. 5C and D), lending additional support to our previous finding that HSulf-1 is a critical determinant for increased sensitivity toward both drugs in vivo (16). More importantly, down-regulation of HSulf-1 in vHNF1 down-regulated clones restored cisplatin resistance to a certain extent.

In the present study, we also determined the expression levels of vHNF1 and HSulf-1 on 501 ovarian carcinomas on a tissue microarray, 20.6% of ovarian tumors on this tissue microarray showed high levels of vHNF1 staining and this was associated with none to lower levels of HSulf-1 expression. Conversely, higher level of HSulf-1 was detected in 61.8% of samples that had negative vHNF1 staining. Moreover, 68.3% of patients with serous ovarian cancer expressed HSulf-1 protein and showed a trend toward improved survival.
vHNF1 might directly or indirectly regulate unknown target genes involved in survival and apoptosis. Our studies indicate that one of these genes is HSulf-1, a putative tumor suppressor that is lost in a substantial portion of ovarian tumors of both clear-cell and non-clear-cell origin. Given the role that HSulf-1 plays in conferring sensitivity to commonly used chemotherapeutic agents, and the fact that it is lost in a higher proportion of ovarian tumors of clear-cell origin, our data suggest that the chemoresistance of clear-cell carcinoma could be associated with the overexpression of vHNF1 acting as a repressor of HSulf-1. Therefore, targeting vHNF1 to up-regulate HSulf-1 could have therapeutic implications in clear-cell carcinoma of ovary.

References


Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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