

IGHG1 promotes motility likely through epithelial-mesenchymal transition in ovarian cancer

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Abstract

Objective: Ovarian cancer (OC) is one of the leading causes of death for female cancer patients. COC166-9 is an OC-specific monoclonal antibody and we have identified immunoglobulin γ -1 heavy chain constant region (IGHG1) as its antigen. We explore the function of IGHG1 in proliferation, apoptosis and motility of OC cells further in this research.

Methods: IGHG1 expression in OC specimens was detected through immunohistochemistry. Real-time quantitative polymerase chain reaction (RT-qPCR) or western blotting assay was used to test IGHG1 expression in OC cells. Viability of OC cells was tested by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Flow cytometry or western blotting assay was used to detect cell cycle and apoptosis. Cellular motility was analyzed by using transwell assay and the markers of epithelial-mesenchymal transition (EMT) were tested through immunoblots.

Results: Although it exerts negligible effect on the viability and apoptosis of OC cells, IGHG1 could promote migration and invasion of malignant cells *in vitro*. Mechanistically, IGHG1 increases the expression of N-cadherin and Vimentin while decreases E-cadherin expression. Additionally, IGHG1 expression in OC specimens is higher relative to the paired normal counterparts. Further analysis demonstrates that the increased IGHG1 expression correlates positively with the lymph node metastasis of OC.

Conclusions: IGHG1 promotes the motility of OC cells likely through executing the EMT program. Increased IGHG1 expression in OC specimens is associated with the lymph node metastasis.

Keywords: IGHG1; ovarian cancer; EMT; invasion; metastasis

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Introduction

Ovarian cancer (OC) ranks as the fifth most common cause of mortality for female cancer patients, accounting for 151,900 deaths worldwide (1,2). The incidence of this devastating malignancy has been rising currently (3-5). The majority of OC patients are diagnosed at advanced stages of disease. Although therapeutics has been developed to

improve treatment outcome, prognosis of the OC patients at late stage remains unfavorable (6). Only one out of four patients with advanced OC could survive for five years after diagnosis (2). One reason for the gloomy survival rate is rapid development of chemo-resistance. For example, 25% of OC patients become unresponsive to platinum drugs within 6 months after the surgery and initial chemotherapy (7). Another reason is metastasis of OC cells, which rules

out surgery and potentially neutralizes traditional chemotherapy strategies (8,9). Therefore, it is critical to uncover molecular mechanisms underlying the two fatal symptoms in OC and develop novel therapeutic methods accordingly.

Identifying unique antigens in malignancy and developing specific antibodies accordingly provide a critical therapeutical option (10). In the late 1980s, the antibody COC166-9 was found to be highly specific in OC (11), and experimental therapy showed that COC166-9 conjugated to cisplatin or adriamycin significantly inhibits xenograft tumor growth in immunocompromised mice (12). Further investigation revealed that immunoglobulin γ -1 heavy chain constant region (IGHG1) is the antigen target of COC166-9 and correlates with poor prognosis and recurrence in OC patients (13). However, the function of IGHG1 in OC progression remains poorly understood.

In this study, we found that IGHG1 expression is higher in OC samples compared with the adjacent normal counterparts. Additionally, increased IGHG1 level is associated with lymph node metastasis. IGHG1 promotes migration and invasion in OC cells likely through modulating epithelial-mesenchymal transition (EMT) program, without affecting proliferation and apoptosis. Together, these results enlighten the roles of IGHG1 in OC progression and provide more evidence for applying COC166-9 in clinical practice.

Materials and methods

Cell culture and reagents

OC cell line Caov-3 and SKOV3, including 3AO, were purchased from the China Military Science Center (Beijing, China). OC3 cells (14) were generously provided by Dr. Hongxia Li (Department of Obstetrics and Gynecology, Beijing Shijitan Hospital of Capital Medical University, China). COC1 and COC1/DDP cells were gifted from Peking Union Medical College Hospital. The ovarian carcinoma cell line HOC1A, derived from poorly differentiated OC surgical specimens, was cultured and preserved in Center of Gynecological Oncology, Department of Obstetrics and Gynecology, Peking University People's Hospital. Caov-3 cells were cultured in dulbecco's modified eagle medium (DMEM) supplemented with 10% fetal calf serum (FBS), 100 U/mL ampicillin, and 100 mg/mL streptomycin. All the other OC cell lines including two derived sublines (SKOV3.ip and COC1/

DDP) were cultured in RPMI1640 containing 10% FBS, 100 U/mL ampicillin, and 100 mg/mL streptomycin. All cells were maintained under the humid conditions (37 °C, 5% CO₂).

Primary antibodies against E-cadherin (sc-7870), N-cadherin (sc-7939), vimentin (sc-32322), and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (sc-59540) were purchased from Santa Cruz Biotechnology (Dallas, TX, USA). The Cleaved Caspase-3 (Asp175) antibody (9661) was purchased from Cell Signaling Technology (MA, USA). An anti-IGHG1 antibody was generated and characterized in Center of Gynecological Oncology, Department of Obstetrics and Gynecology, Peking University People's Hospital. Three specific siRNAs against IGHG1 were purchased from Invitrogen (Carlsbad, CA, USA). 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and propidium iodide (PI) were purchased from Sigma-Aldrich (St. Louis, Missouri, USA).

RNA and real-time quantitative polymerase chain reaction (RT-qPCR)

Total RNA was extracted from cells using the standard Trizol (Invitrogen) procedure. RNA quality was assessed and treated with a TURBO DNA-free Kit (Invitrogen). SuperScript III (Invitrogen) was used to prepare cDNA. Quantitative PCR was performed using the TransScript II Green One-Step RT-qPCR SuperMix (TransGen Biotech, Beijing, China). Primers used to detect IGHG1 were: 5'-GCAGCCGGAGAACAACACTACA-3' (forward) and 5'-TGGTTGTGCAGAGCCTCATG-3' (reverse). Primers for the GAPDH internal control were: 5'-TGTTGCCATCAATGACCCCTT-3' (forward) and 5'-CTC CACGACGTACTCAGCG-3' (reverse). The abundance of IGHG1 mRNA was evaluated using the 2^{- $\Delta\Delta$ Ct} method.

Plasmids, RNAi and transfection

IGHG1 was cloned into pcDNA3.1 (pcDNA3.1-IGHG1) and the construct was verified by sequencing (Invitrogen). Plasmids or a pool of three siRNAs (100 nmol/L in total) were transiently transfected into OC cells using ScreenFect A (Incella, Eggenstein-Leopoldshafen, Germany) according to the manufacturer's instructions.

Proliferation assay

MTT assay and flow cytometry were used to detect the

viability of OC cells. The same number of cells (6×10^3 cells/well) was plated into 96-well dish and OD₄₉₀ was detected in three consecutive days. As for cell cycle assay, cells were harvested using trypsin and fixed using 75% ethanol. PI was added into the suspended cells before analysis. MTT assays and flow cytometry were carried out twice independently and five biological replicates were involved in each assay.

Apoptosis assay

We examined apoptosis in Caov-3 or OC3 cells using the FITC Annexin V/Dead Cell Apoptosis Kit (Invitrogen), according to the manufacturer's instructions. The Annexin V-PI assay was performed twice independently and three biological replicates were involved in each assay. The levels of cleaved-Caspase3 in IGHG1-manipulated Caov-3 and OC-3 cells were detected by western blotting.

Transwell assay

Cellular migration and invasion *in vitro* were tested as previously described (15). In invasion assay, 100 μ L FBS-free DMEM or RPMI1640 containing 3.6 μ L Matrigel (BD, Franklin Lakes, New Jersey, USA) was added into the inserts. After 2 h, 1×10^5 cells were seeded into each insert and incubated for 8 h. The inserts were then harvested, fixed and stained with crystal violet. Five fields were selected randomly and cells that had penetrated the membrane were counted. Data are shown as $\bar{x} \pm s$.

Immunoblot assay

Proteins were extracted from cells with lysis buffer (100 mmol/L NaCl, 10 mmol/L EDTA (pH 8.0), 50 mmol/L Tris-Cl (pH 8.0) and 0.5% (v/v) Triton X-100) containing protease inhibitor (Roche, Basel, Switzerland). Protein concentration was determined using BCA method (Thermo Fisher Scientific, MA, USA). Total proteins were separated on SDS-PAGE gel and transferred to PVDF membranes. GAPDH was used as the loading control.

Immunohistochemistry (IHC)

IHC assay was performed as previously described (16). All experiments on OC samples were approved by the Institute Research Medical Ethics Committee of Peking University People's Hospital. Results were analyzed independently by two pathologists from the Department of Pathology in Peking University People's Hospital (Beijing, China).

Statistical analysis

Except the IHC assay, all experiments were performed independently twice at least. Two-tailed Student's *t*-test or Chi-square test was used to analyze the significance of data. Data are presented as $\bar{x} \pm s$. GraphPad Prism 6 (GraphPad Software, Inc., CA, USA) was used to draw bar charts. In bar graphs, *, ** and *** indicate $P < 0.05$, $P < 0.01$ and $P < 0.001$, respectively.

Results

IGHG1 expression in OC specimens and cell lines

First, we examined IGHG1 expression in 94 pairs of OC and adjacent normal tissues, showing that IGHG1 expressions in malignant tissues were dramatically increased compared with the adjacent normal counterparts (Figure 1A). Chi-square test was utilized to compare the differences in IGHG1 protein expression between OC tissues and adjacent noncancerous tissues ($P < 0.05$). Further analysis revealed that the elevated IGHG1 expression correlated with the lymph node metastasis of OC ($P = 0.04$, Figure 1B), implying that IGHG1 probably involves in regulating motility of OC cells. Then we tested the endogenous expression of IGHG1 in a panel of OC cell lines using quantitative PCR, among which three cell lines (Caov-3, SKOV3, and SKOV3.ip) possessed higher IGHG1 levels than the rest ones (COC1, COC1/DDP, ES-2, OC3, and 3AO) (Figure 1C).

Two cell lines with high IGHG1 expressions (Caov-3 and SKOV3) and two with low IGHG1 levels (OC3 and 3AO) were used for analyzing the functions of IGHG1 in OC. We introduced a pool of three specific siRNAs against IGHG1 into Caov-3 and SKOV3 cells respectively to silence IGHG1 expressions significantly (Figure 2A, B). We also transfected plasmid pcDNA3.1-IGHG1 and the control plasmid into OC3 and 3AO cells respectively, and the increased IGHG1 levels were then confirmed by using quantitative PCR and immunoblot assay (Figure 2C, D).

IGHG1 does not affect the proliferation of OC cells

To test whether IGHG1 would affect the proliferation of OC cells or not, we firstly used MTT assay to detect the viability of OC cells within three days. MTT assays showed that decreased expressions of IGHG1 in Caov-3 and SKOV3 cells did not change the proliferation in these treated cells compared with the control ones. Likewise, elevated IGHG1 level failed to influence the growth of

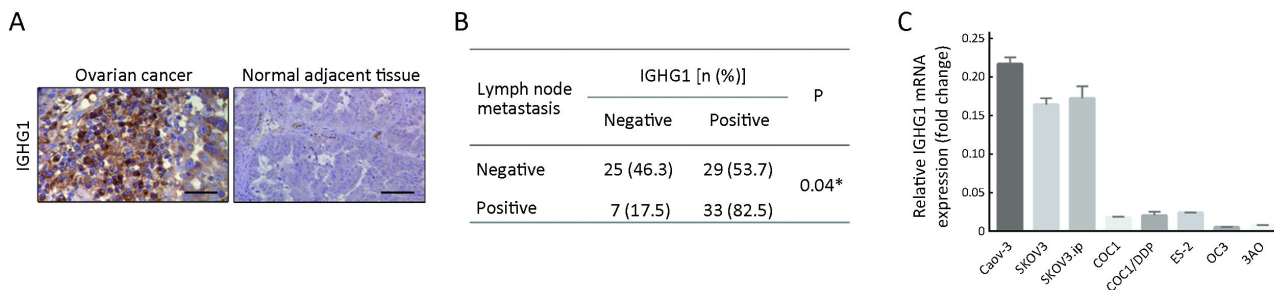


Figure 1 Immunoglobulin γ -1 heavy chain constant region (IGHG1) expression in ovarian cancer (OC) samples and cell lines. (A) IGHG1 expressions in OC tissues are aberrantly increased compared with the adjacent normal tissues (N=94). Scale bars indicate 100 μ m. Chi-square test was utilized to compare the differences in IGHG1 protein expression between OC tissues and adjacent noncancerous tissues (P<0.05); (B) IGHG1 correlates with the lymph node metastasis of OC. Chi-square test was utilized to compare the differences in IGHG1 protein expression between OC patients with lymph node metastasis or not (P=0.04); (C) Screen of IGHG1 expressions in eight OC cell lines, showing that Caov-3, SKOV3 and SKOV3.ip cell lines possess high IGHG1 expression while the other five OC cell lines have low IGHG1 levels. The data are expressed as $\bar{x}\pm s$.

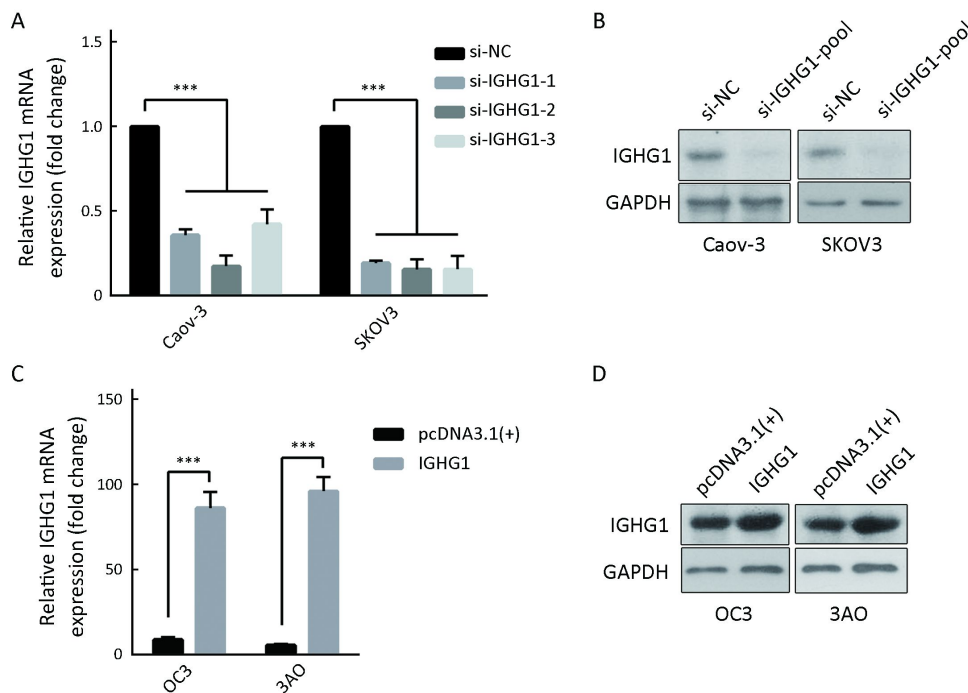


Figure 2 Expressions of immunoglobulin γ -1 heavy chain constant region (IGHG1) are silenced or overexpressed in ovarian cancer (OC) cells. (A, B) Decreased expressions of IGHG1 were detected using real-time quantitative polymerase chain reaction (RT-qPCR) and immunoblot assays in Caov-3 and SKOV3 cells, which were transfected with a pool of three siRNAs (100 nmol/L in total) respectively; (C, D) Increased levels of IGHG1 were examined in OC3 and 3AO cells, which were transiently transfected with pcDNA3.1-IGHG1 and pcDNA3.1 respectively, by RT-qPCR and immunoblot western blotting assays. The data are expressed as $\bar{x}\pm s$. ***, P<0.001.

OC3 cells as well. The results are reported as $\bar{x}\pm s$, and statistical significance was assessed by two-tailed Student's *t* tests with the level of significance set at P<0.05. The experiments were performed twice independently with five biological replicates. Increased or decreased expression of

IGHG1 did not influence growth of the manipulated cells compared with those control cells (P>0.05) (Figure 3A). Furthermore, silence of IGHG1 in both Caov-3 and SKOV3 cells failed to alter the cell cycle distribution (P>0.05) (Figure 3B).

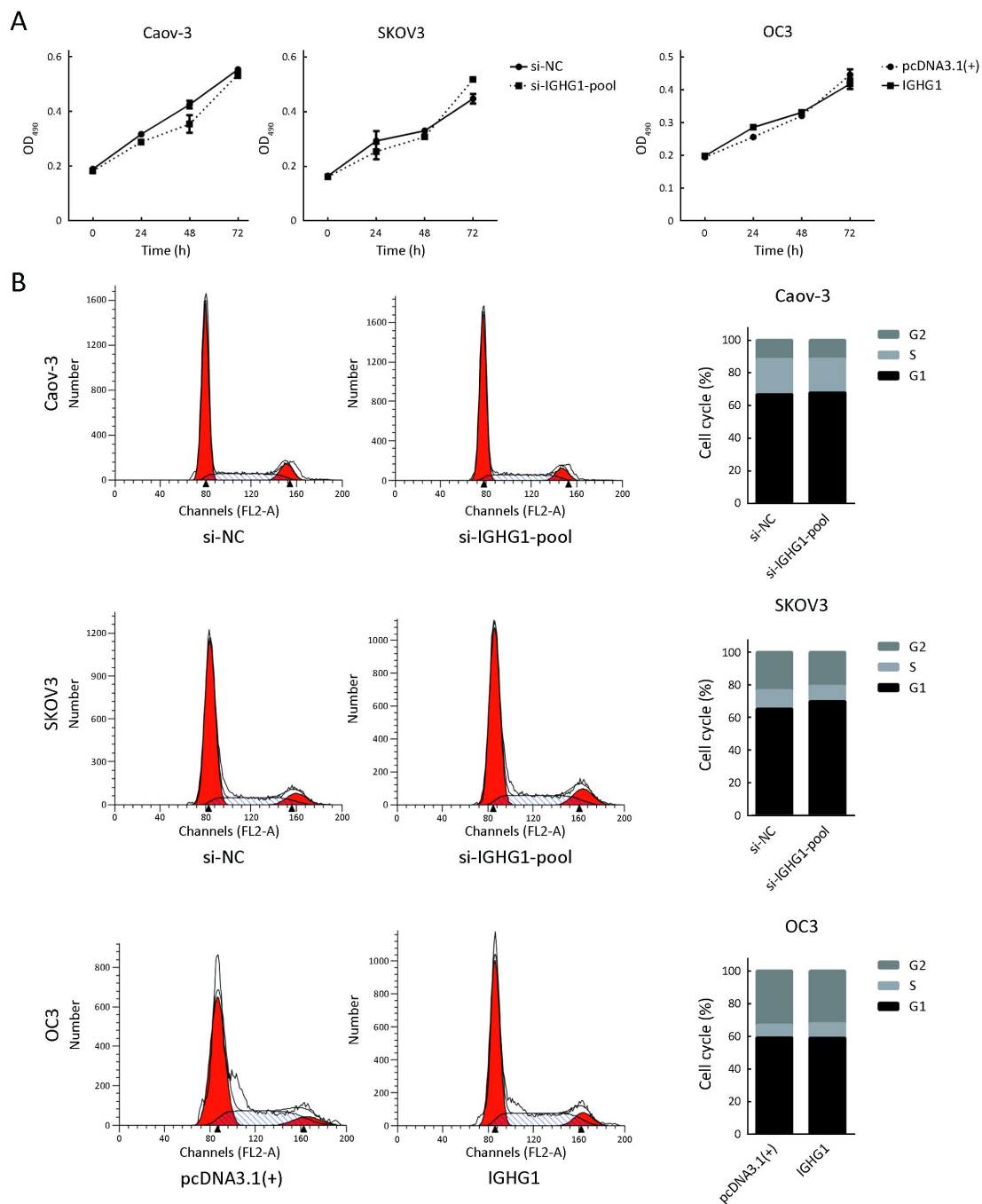


Figure 3 Immunoglobulin γ -1 heavy chain constant region (IGHG1) does not affect the proliferation of ovarian cancer (OC) cells. (A) 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays show that decreased expressions of IGHG1 in Caov-3 and SKOV3 cells does not change the proliferation in these treated cells compared with the control ones ($P>0.05$). Likewise, elevated IGHG1 level fails to influence the growth of OC3 cells as well ($P>0.05$). OC cells (6×10^3 cells/well) were plated into 96-well dishes and OD₄₉₀ were detected at the indicated time points. Each data come from five parallel wells. The experiments were performed twice independently. The results are reported as $\bar{x} \pm s$, and statistical significance was assessed by two-tailed Student's t tests with the level of significance set at $P<0.05$; (B) Flow cytometry results show that either silence of IGHG1 in Caov-3 and SKOV3 cells or overexpression of IGHG1 in OC3 cells does not alter cell cycle distribution ($P>0.05$).

IGHG1 does not influence the apoptosis of OC cells

In order to test the potential effect of IGHG1 on apoptosis, we detected the apoptosis rate in OC cells using PI & Annexin V assay. The assay was performed twice independently and three biological replicates were involved in each assay. Neither silence of IGHG1 in Caov-3 cells nor overexpression of IGHG1 in OC3 cells influences the apoptosis in these manipulated cells, comparing with the control counterparts ($P>0.05$). *Figure 4* shows one representative result. Knockdown of IGHG1 in Caov-3 cells exerted little effect on apoptosis (*Figure 4A*). Likewise, the increased IGHG1 levels in OC3 cells neither promoted nor inhibited apoptosis relative to those control counterparts (*Figure 4B*). The levels of cleaved caspase 3 in Caov-3 and OC-3 cells were detected by western blotting, and no alterations were observed between the control and

IGHG1-manipulated cells (*Figure 4C, D*). The experiments were performed twice independently.

IGHG1 promotes motility of OC cells

Since IGHG1 expression is associated with the lymph node metastasis, then we examined whether IGHG1 promoted the motility of OC cells or not. We found that decreased IGHG1 expression in SKOV3 cells impaired *in vitro* migration and invasion relative to the control cells (*Figure 5A*). On the other side, overexpression of IGHG1 stimulated more 3AO cells to penetrate the transwell membrane in both migration and invasion assays (*Figure 5B*).

As EMT program underlies the enhanced motility and metastasis of OC cells (17), we then examined whether or not IGHG1 promoted motility of OC cells through modulating EMT. As expected, E-cadherin level increased while N-cadherin and Vimentin decreased in SKOV3 cells

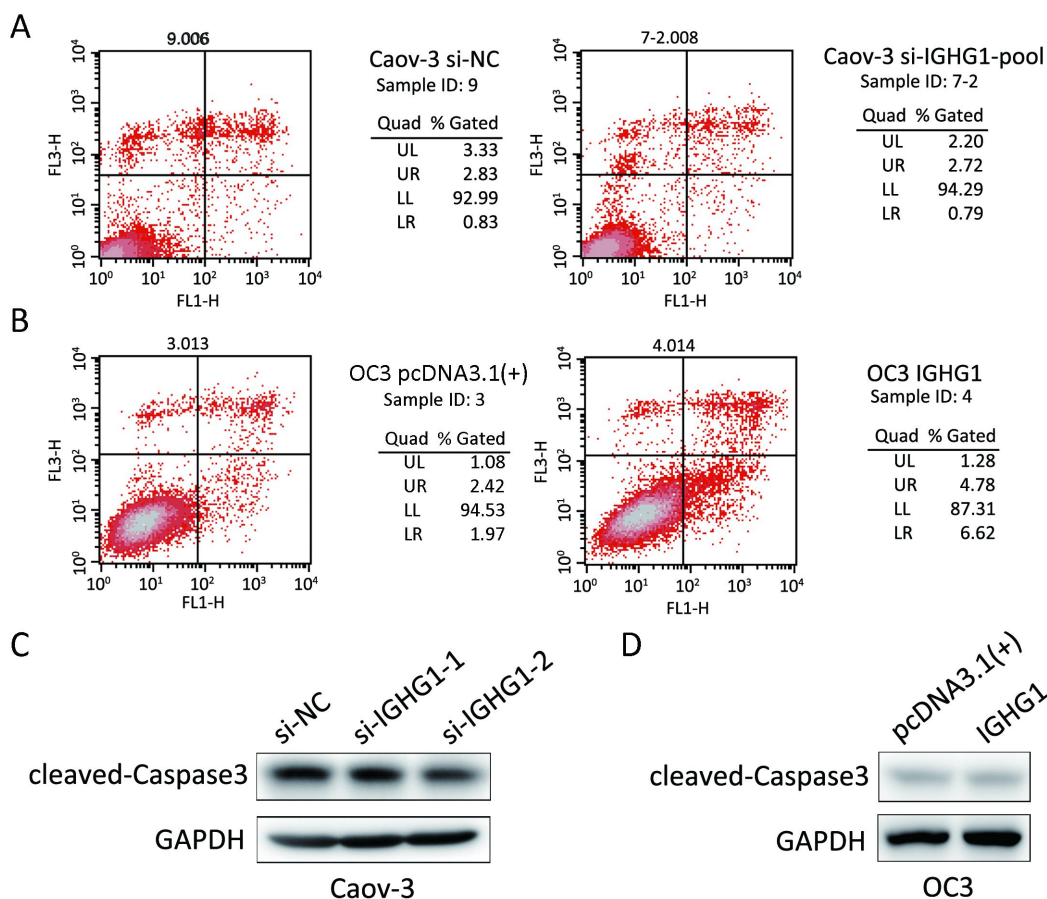


Figure 4 Immunoglobulin γ -1 heavy chain constant region (IGHG1) does not affect the apoptosis in ovarian cancer (OC) cells. (A, B) Neither silence of IGHG1 in Caov-3 cells nor overexpression of IGHG1 in OC3 cells influences the apoptosis in these manipulated cells, comparing with the control counterparts ($P>0.05$). The figure shows one representative result; (C, D) The levels of cleaved-Caspase3 in Caov-3 and OC-3 cells, no alterations were observed between the control and IGHG1-manipulated cells.

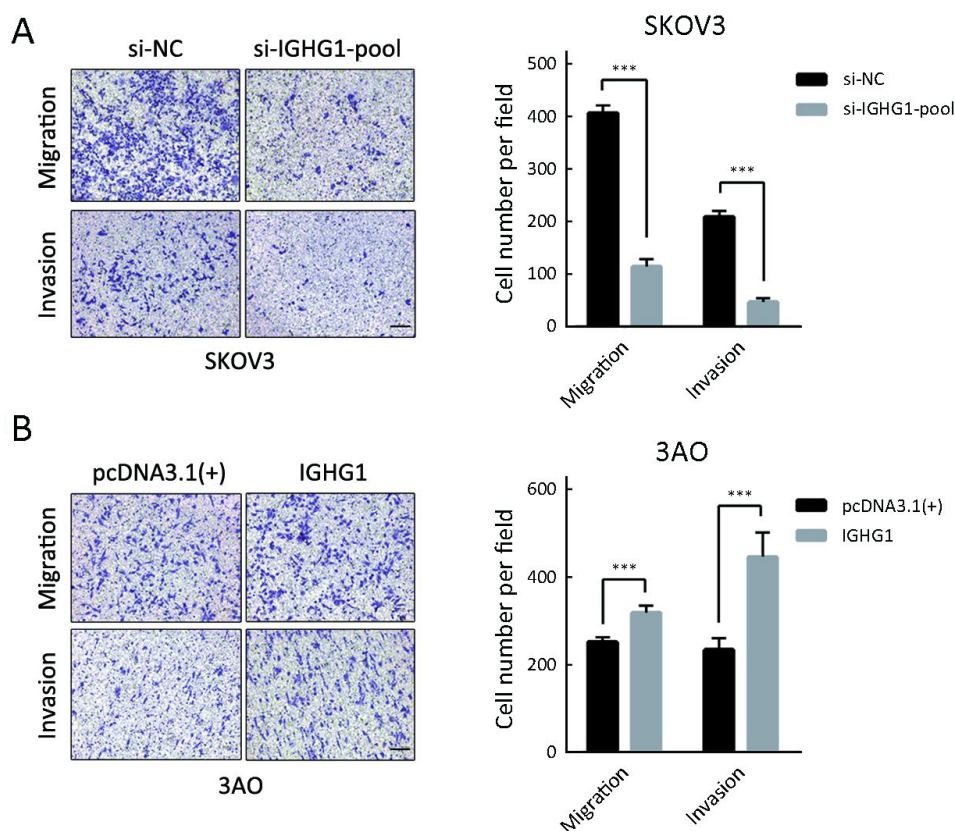


Figure 5 Immunoglobulin γ -1 heavy chain constant region (IGHG1) promotes the motility of ovarian cancer (OC) cells. (A) Decreased IGHG1 level in SKOV3 cells impairs migration and invasion *in vitro*; (B) On the other hand, overexpression of IGHG1 in 3AO cells enhances the cellular motility. SKOV3 or 3AO cells (10^4) were seeded in the inserts and the cells were incubated for 8 h before being analyzed. Scale bars indicate 100 μ m. ***, $P < 0.001$.

owing to silencing of IGHG1 (Figure 6A). Vice versa, overexpression of IGHG1 in 3AO cells promoted the expression of N-cadherin and Vimentin while inhibited E-cadherin expression (Figure 6B). Collectively, these data demonstrate that IGHG1 enhances the motility of OC cells likely through EMT.

Discussion

IGHG1 has recently been determined as the antigen of the antibody COC166-9 and aberrantly increased expression of IGHG1 correlates with poor prognosis in OC patients (13). We thereby set out to explore the function of IGHG1 in OC progression. Ji *et al.* reported that IGHG1 promotes the proliferation of HOC1A cells but exerts negligible effects on the growth of Caov-3 cells (13). However, overexpression of IGHG1 did not affect the proliferation or apoptosis of OC cells in this study. This contradiction is probably attributable to differences among the cellular

backgrounds or experimental settings. The addition of IGHG1 into the cultured Caov-3 cells failed to alter proliferation probably because the increased IGHG1 level could not activate the relevant signaling pathways. Moreover, the result of IGHG1 treatment in HOC1A cells alone cannot represent other OC cells. Collectively, these results suggest the complex effects of IGHG1 on the proliferation of OC cells. More evidence is required to address this question, such as *in vivo* growth assays in immunocompromised mice.

Based on the strong correlation between IGHG1 overexpression and OC recurrence (13), we tested whether or not IGHG1 promoted the ability of OC cells to undergo invasion and metastasis, these processes are responsible for almost 90% of cancer-induced deaths (18). We found that IGHG1 overexpression promotes the migration and invasion of OC cells *in vitro* and positively correlates with the lymph node metastasis *in vivo*. We showed that IGHG1 overexpression enhances OC cells motility through

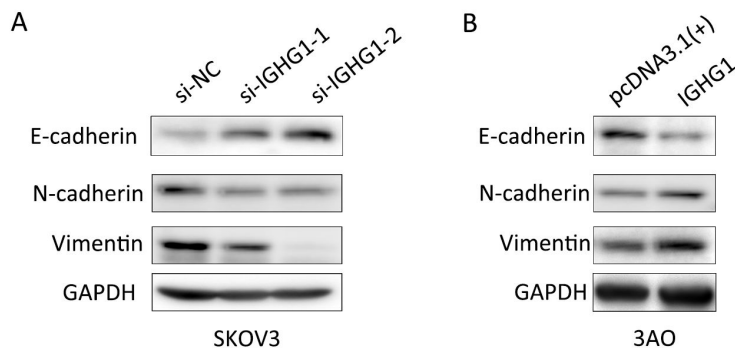


Figure 6 Immunoglobulin γ -1 heavy chain constant region (IGHG1) stimulates the expressions of key epithelial-mesenchymal transition (EMT) markers. (A) Silence of IGHG1 decreases the expression of N-cadherin and Vimentin while induces the expression of E-cadherin in SKOV3 cells; (B) In 3AO cells, IGHG1 overexpression reduces E-cadherin level whereas increases N-cadherin and Vimentin levels.

modulating the expressions of key EMT markers. The critical roles of EMT in cancer stemness, invasion-metastasis cascade, and resistance to therapy are well documented in a wide range of cancers including OC (19-21). Moreover, EMT in OC is regulated by a few molecules and signaling pathways (22-25). Although the mechanistic details underlying the IGHG1-induced EMT have not been determined yet, we speculate that IGHG1 also contributes to stemness and chemo-resistance in OC cells. Further investigations are thus needed to obtain more details about how IGHG1 regulates EMT and the invasion-metastasis cascade in OC.

Conclusions

Our results show that IGHG1 facilitates migration and invasion and regulates several critical EMT markers in OC cells. Impeding the invasion and metastasis of OC cells is a clinical challenge currently; therefore, it is urgent to identify potent diagnostic and therapeutic markers (19). More importantly, COC166-9, which targets IGHG1 specifically, has been showed to be highly effective in the experimental therapies of OC. Targeting IGHG1 is thereby a promising approach to treat metastasis and chemotherapy resistance in OC.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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