Original Article

Identification of solute-carrier family 27A molecules (SCL27As) as a potential biomarker of ovarian cancer based on bioinformatics and experiments

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Background: Ovarian cancer is one of the 3 major gynecological malignancies with high mortality, poor prognosis, and lack of specific diagnostic and prognostic markers. Solute-carrier family 27A molecules (SCL27As) play a crucial role in multiple malignant tumors via the regulation of long-chain fatty acid uptake and subsequent regulation of lipid metabolism. To date, the specific mechanisms and roles of SCL27As in epithelial ovarian cancer (EOC) have remained unclear.

Methods: The Oncomine and Gene Expression Profiling Interactive Analysis (GEPIA) databases and the Kaplan-Meier plotter were used to explore the differential expression and the prognostic value of SCL27As in EOC. The expression of *SCL27A6* in 20 normal ovarian tissues and 120 ovarian cancer tissues was detected by immunohistochemistry (IHC). Cell Counting Kit-8 (CCK8) assay and colony-forming experiments were conducted to evaluate the role of *SCL27A6* in the proliferation of ovarian cancer cells, so as to verify the clinical application value of *SCL27A6* in the diagnosis and prognosis of ovarian cancer. We extracted the data of *SCL27A6* for multiple bioinformatics analysis to identify the potential regulatory mechanism of *SLC27A6*.

Results: The expression levels of *SLC27A1* and *SLC27A6* were significantly decreased in ovarian cancer tissues. Prognostic analysis showed that *SLC27A2*, *SLC27A4*, *SLC27A5*, and *SLC27A6* expression levels were significantly correlated with overall survival (OS) in EOC patients. Moreover, the expression of the SLC27A6 protein was decreased in EOC tissues, which was related to the prognosis. Additionally, knocking down the expression of *SLC27A6* could significantly enhance the malignant biological behavior of ovarian cancer cells. The *SLC27A6* gene may be involved in the proteasome, cell cycle, Hippo signaling pathway, and so on.

Conclusions: This study revealed the abnormal expression and prognostic value of *SLC27As* in EOC. In addition, it was highlighted that *SLC27A6* may be a novel biomarker for the diagnosis and prognostication of EOC patients.

Keywords: Solute-carrier family 27A molecules (SCL27As); SLC27A6; ovarian cancer; prognosis; biomarker

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Introduction

Epithelial ovarian cancer (EOC) is one of the leading causes of gynecological malignancy-related death worldwide. In 2018, there will be approximately 22,240 new cases of ovarian cancer diagnosed and 14,070 ovarian cancer deaths in the US (1). It has a high mortality rate, accounting for 3.3% of all deaths from malignant diseases (2,3). Although surgical treatment, platinum-based chemotherapy (4), immune checkpoint inhibitors, and poly-ADP ribose polymerase (PARP) inhibitors (5) have improved the prognosis of patients to a certain extent, the 5-year survival rate of patients with advanced EOC is only 20–30% (6). Therefore, it is of clinical significance to screen reliable markers to study their roles in the development and progression of EOC and to determine the diagnosis and prognosis of such patients more accurately.

Tumor metabolic reprogramming is one of the hallmarks of malignant tumors (7) and includes enhanced aerobic glycolysis, enhanced lipid and protein synthesis, and enhanced glutamine uptake and catabolism (8,9). Several recent studies have shown that lipid metabolism reprogramming plays an important role in the tumor microenvironment and participates in regulating the malignant biological behaviors of cancer cells (10-12). Serum lipid profiling analysis showed that lipids were differentially expressed among patients with EOC, healthy controls, and benign ovarian tumors, and those lipids could be used for EOC diagnosis (13). In advanced EOC, the lipid metabolism of tumor cells in the ascites microenvironment is disordered, which enhances the invasiveness of tumor cells. In addition, targeting lipid metabolism pathways can effectively prevent EOC peritoneal metastasis (14). Therefore, lipid metabolism-related molecules play a crucial role in the development of EOC and have potential for clinical applications as biomarkers.

Solute-carrier family 27A molecules (SCL27As) are integral transmembrane proteins that play a crucial role in lipid metabolism via the regulation of long-chain fatty acid uptake. The SCL27As (SCL27A1-6) also play a vital role in the progression of malignant tumors. The downregulation of *SLC27A2* could lead to cisplatin resistance in lung cancer via the Bmi1-ABCG2 pathway (15), and *SLC27A2* also affects chemoresistance in ovarian cancer (16). In breast cancer (17) and clear cell renal cell carcinoma (18), *SLC27A4* acts as an oncogene by regulating tumorigenesis and tumor progression. However, the function and potential clinical value of SLC27As in ovarian cancer are still unknown.

Here, we analyzed the expression level and prognostic value of SLC27As in EOC. The protein level and function of *SLC27A6* were analyzed based on clinical samples and experiments. Finally, the regulatory mechanism of *SLC27A6* was explored via bioinformatics analysis. Overall, the results suggested that *SLC27A6* plays a crucial role in EOC and is a potential biomarker for EOC patients.

We present the following article in accordance with the REMARK reporting checklist (available at https://dx.doi.org/10.21037/atm-21-3026).

Methods

Messenger RNA expression level and the prognostic value of SLC27As in ovarian cancer

The Oncomine dataset (https://www.oncomine.org/) was used to explore the messenger RNA (mRNA) expression level of SLC27As (1-6) in ovarian cancer tissue and normal tissue. The criteria were as follows: (I) cancer type: ovarian cancer; (II) thresholds: $P<0.05$, fold change (fc) >1.5, and gene rank = top 10%.

The Gene Expression Profiling Interactive Analysis (GEPIA) dataset (http://gepia.cancer-pku.cn/) was used to analyze the mRNA expression level of SLC27As in ovarian cancer tissue and normal tissue in the The Cancer Genome Atlas-Ovarian Cancer (TCGA-OV) dataset and Genotype-Tissue Expression (GTEx) dataset.

The Kaplan-Meier plotter dataset (19) (http://kmplot.com/) was used to analyze the prognostic value of SLC27As in patients with ovarian cancer by hazard ratios (HRs) with 95% confidence intervals (CIs), and the log rank P value.

Genomic alteration analysis of SLC27A6 in ovarian cancer

We analyzed genetic alterations of *SLC27A6* in ovarian cancer with the cBioPortal dataset (20) (https://www.cbioportal.org).

Immunohistochemistry (IHC) analysis

A total of 20 cases of normal ovarian tissue and 120 cases of ovarian cancer tissue were collected from patients who underwent operations from June 2018 to December

2020 at the the First Affiliated Hospital of China Medical University. This study was approved by the Ethics Committee of the the First Affiliated Hospital of China Medical University (No.: AF-SOP-07-1.1-01) and all patients provided written informed consent. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The tissues were fixed in 10% formalin, embedded in paraffin, and processed as 4 μm continuous sections. IHC staining was performed according to the manufacturer's instructions (UltraSensitive™ SP; MXB, Fuzhou, China). The antibody was anti-SLC27A6 (1:100; PA5-34544; Invitrogen, Carlsbad, CA, USA). Each sample was independently assessed by 2 pathologists and scored using a semiquantitative scoring system. The histoscores ranged from zero (minimum) to 300 (maximum).

Cell culture

The human ovarian cancer cell line A2780 was obtained from the China Infrastructure of Cell Line Resources and cultured in Dulbecco's modified Eagle medium (DMEM) with 10% fetal bovine serum (FBS) at 37 ℃ in a humidified 5% CO_2 incubator.

Cell Counting Kit-8 (CCK-8) assay

The A2780 cells (1,500/well) were cultured in 96-well plates and transfected with negative control-small interfering RNA (NC-siRNA) and *SLC27A6*-specific siRNA (Suzhou GenePharma Co., Ltd., Suzhou, China). Cells were cultured with CCK-8 solution (C0038, Beyotime, Shanghai, China) for another 2 h after 0, 24, 48, or 72 h. Cell viability was expressed as an optical density (OD) value at 450 nm. Results are representative of 3 separate experiments; data are expressed as the mean ± standard deviation, and *P<0.05.

Colony-forming experiments

To explore the effect of *SLC27A6* expression on human ovarian cancer cell proliferation, A2780 cells (500/well) transfected with NC-siRNA or siRNAs were plated in 12-well culture dishes. After 2 weeks, the number of colonies was counted. Results are representative of 3 separate experiments; data are expressed as the mean ± standard deviation, and *P<0.05.

Functional analysis of SLC27A6

The SLC27A6-related differentially expressed genes were obtained from the LinkedOmics database (http://www.linkedomics.org/) (20). The R package "cluster profiler" was used to analyze the above genes through Gene Ontology (GO) enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis. A P value <0.05 was defined as a meaningful enrichment analysis result.

Statistical analysis

Statistical comparisons between 2 groups were calculated using Student's 2-tailed *t*-test, and P values <0.05 were considered statistically significant. The median value of gene expression was chosen for cutpoint in Kaplan-Meier analysis.

Results

mRNA expression level of SLC27As in ovarian cancer tissue and normal tissue based on public databases

We first compared the expression differences of SLC27As between ovarian cancer tissues and normal ovarian tissues based on the Oncomine database. As shown in *Figure 1A*, the expression levels of *SLC27A1*, *SLC27A4*, and *SLC27A5* were not significantly different between ovarian cancer cells and normal ovarian cells. In Yoshihara ovarian statistics (21), *SLC27A2* was up-regulated in ovarian cancer tissues (fc =3.840, P=7.86E-5) compared with normal ovarian tissues. In TCGA ovarian statistics, the expression level of *SLC27A2* was decreased in ovarian cancer tissue (fc =–8.115, P=3.85E-6) compared with normal ovarian tissue. In Bonome ovarian statistics (22), *SLC27A3* was over-expressed in ovarian cancer tissues (fc =1.971, P=7.73E-9). In TCGA ovarian statistics (fc =–9.222, P=2.46E-8) and Lu ovarian statistics (23) (fc =–1.815, P=8.59E-4), the expression level of *SLC27A6* was down-regulated in ovarian cancer tissues. Due to the small number of normal ovarian tissue samples in the TCGA dataset, we included the GTEx dataset for further analysis. As shown in *Figure 1B-1G*, *SLC27A1* and *SLC27A6* expression were down-regulated in ovarian cancer tissues more than in normal tissues. *SLC27A2*, *SLC27A3*, *SLC27A4*, and *SLC27A5* expression

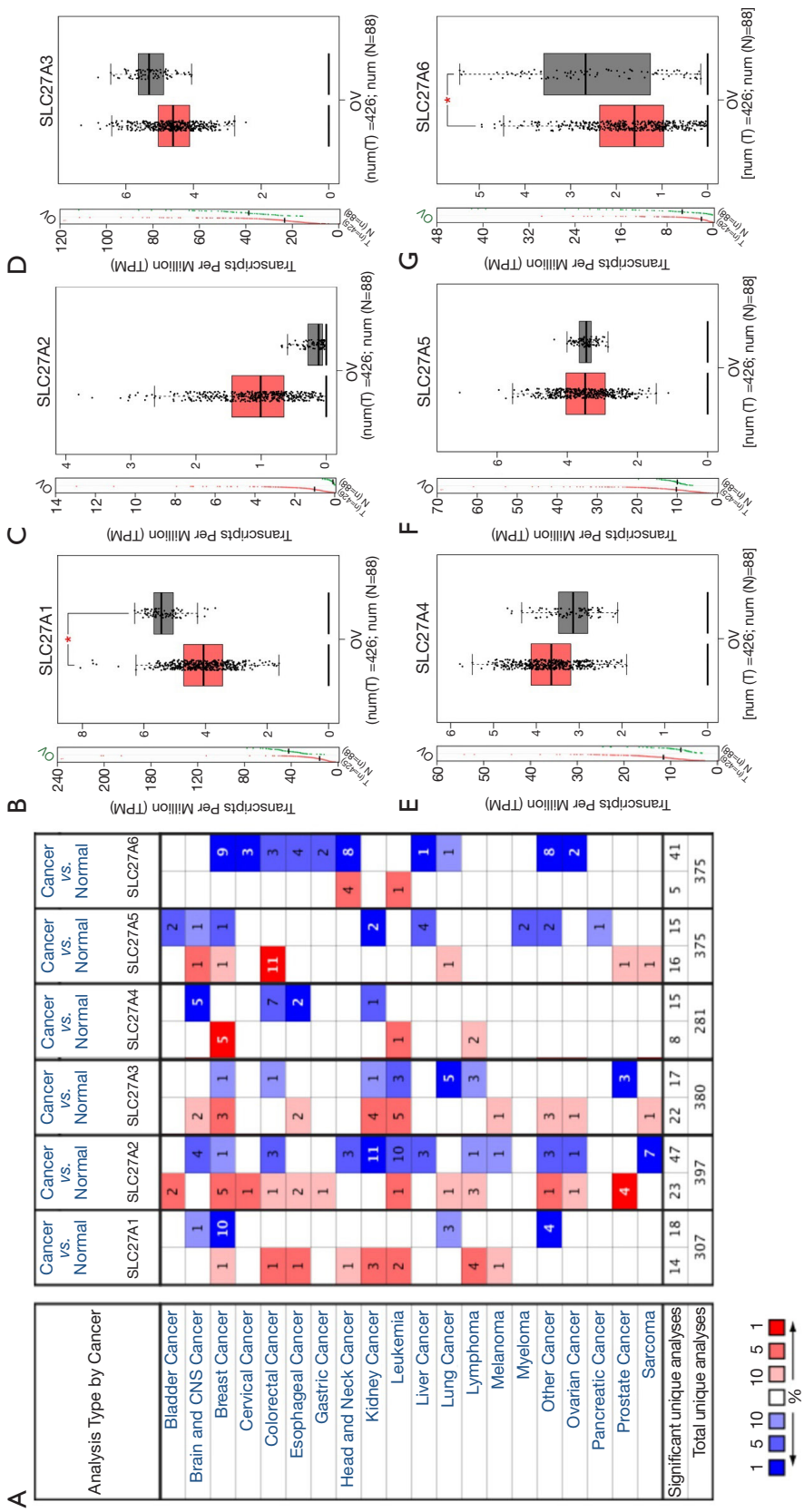

Figure 1 Expression level of SLC27As in ovarian cancer tissue and normal tissue based on public databases. (A) The expression level of SLC27As in different types of cancer based on the Oncomine database. (B-G) The expression level of SLC27As in ovarian cancer tissue and normal tissue based on the TCGA and GTEx databases. *P<0.05. SCL27As, solute-carrier family 27A molecules; TCGA, The Cancer Genome Atlas; GTEx, Genotype Tissue Expression.

were no difference.

Prognostic value of SLC27As in patients with ovarian cancer

Next, we analyzed the prognostic value of SLC27As in ovarian cancer based on the Kaplan-Meier plotter dataset (*Figure 2A-2F*). The expression levels of *SLC27A1* and *SLC27A3* had no significant correlation with the overall survival (OS) of patients with ovarian cancer. Low expression of *SLC27A2* (HR=0.74, 95% CI: 0.64 to 0.86, P=9.7e-5), *SLC27A5* (HR=0.86, 95% CI: 0.74 to 0.99, P=0.041) and SLC27A6 (HR=0.82, 95% CI: 0.72 to 0.94, P=0.0055) was significantly correlated with a poor OS in patients with ovarian cancer. Higher expression of *SLC27A4* (HR =1.35, 95% CI: 1.1 to 1.66, P=0.0034) was significantly correlated with poor OS in patients with ovarian cancer. As shown in *Figure 2G*, *SLC27A6* was selected for subsequent analysis due to its significant differential expression and potential prognostic value.

Prognostic value of SLC27A6 in a subgroup of patients with ovarian cancer

Patients with different clinicopathological characteristics have different treatment strategies and prognoses. Next, we analyzed the prognostic value of *SLC27A6* in a subgroup of patients with ovarian cancer (*Figure 3A-3F*). The expression level of *SLC27A6* had no significant correlation with the OS of early-stage ovarian cancer patients (stage 1+2) or TP53-mutated ovarian cancer patients. The expression level of *SLC27A6* had no significant correlation with OS, regardless of whether the tumor was low grade (grade 1+2) or high grade (grade 3). Low expression of *SLC27A6* showed significant correlations with poor OS in advanced ovarian cancer patients (stage 3+4) and TP53 wild-type ovarian cancer patients.

Validation of the protein expression and prognostic performance of SLC27A6 in patients with ovarian cancer

To further verify the clinical value of *SLC27A6* in the ovaries, we used IHC to detect the expression level of *SLC27A6* in 20 normal ovarian tissue samples and 120 ovarian cancer tissue samples. Representative staining pictures of *SCL27A6* in normal ovarian tissue and ovarian cancer tissue are shown in *Figure 4A*. Further analysis showed that the IHC score of *SLC27A6* in ovarian cancer tissue was significantly lower than that in normal ovarian tissue (*Figure 4B*). In addition, there was no significant difference in the IHC score of *SLC27A6* between low-grade ovarian cancer and high-grade ovarian cancer (*Figure 4C*).

According to the IHC score of *SLC27A6*, we divided patients with ovarian cancer into an SLC27A6-positive group and an SLC27A6-negative group. The KM analysis showed that compared with the SLC27A6-positive group, the ovarian cancer patients in the SLC27A6-negative group had a worse OS (*Figure 4D*, P<0.001). Further subgroup analysis (*Figure 4E-4G*) showed that lower *SLC27A6* expression was associated with a poor OS of patients with high-grade ovarian cancer (P=0.013) but was not related to the OS of patients with low-grade ovarian cancer (P=0.129). Further analysis showed that the expression of *SLC27A6* was related to the OS of ER (+), ER (–), P53 (+), and P53 (–) ovarian cancer patients.

Functional validation of SLC27A6 in ovarian cancer cells

Next, we used specific siRNA to knock down the expression of *SLC27A6* in A2780 cells to explore its effect on ovarian cancer cells. The CCK-8 and colony formation experiments showed that after knocking down the expression of *SLC27A6*, the proliferation ability of A2780 cells was significantly upregulated (*Figure 5A,5B*). Further Transwell experiments showed that after knocking down *SLC27A6*, the migration ability of A2780 cells was significantly upregulated (*Figure 5C*). These results indicate that *SLC27A6* may be a tumor suppressor gene of ovarian cancer.

Genomic alterations of SLC27A6 in ovarian cancer

Genome mutations are closely related to the occurrence and development of tumors (24). We evaluated the frequency of genetic variation of *SLC27A6* using the cBioPortal database. Genetic variations of *SLC27A6* showed rates of 1.54% (amplification: 0.51%, deep deletion: 1.03%) in the TCGA cohort, 1.37% (mutation: 0.17%, amplification: 0.51%, deep deletion: 0.68%) in the TCGA PanCancer cohort, and 0.41% (amplification: 0.3%, deep deletion: 0.3%) in the TCGA pub cohort (*Figure 6*).

Functional analysis of SLC27A6 in ovarian cancer

We used the LinkedOmics database to obtain 5,338 genes significantly related to *SLC27A6* expression in the TCGA

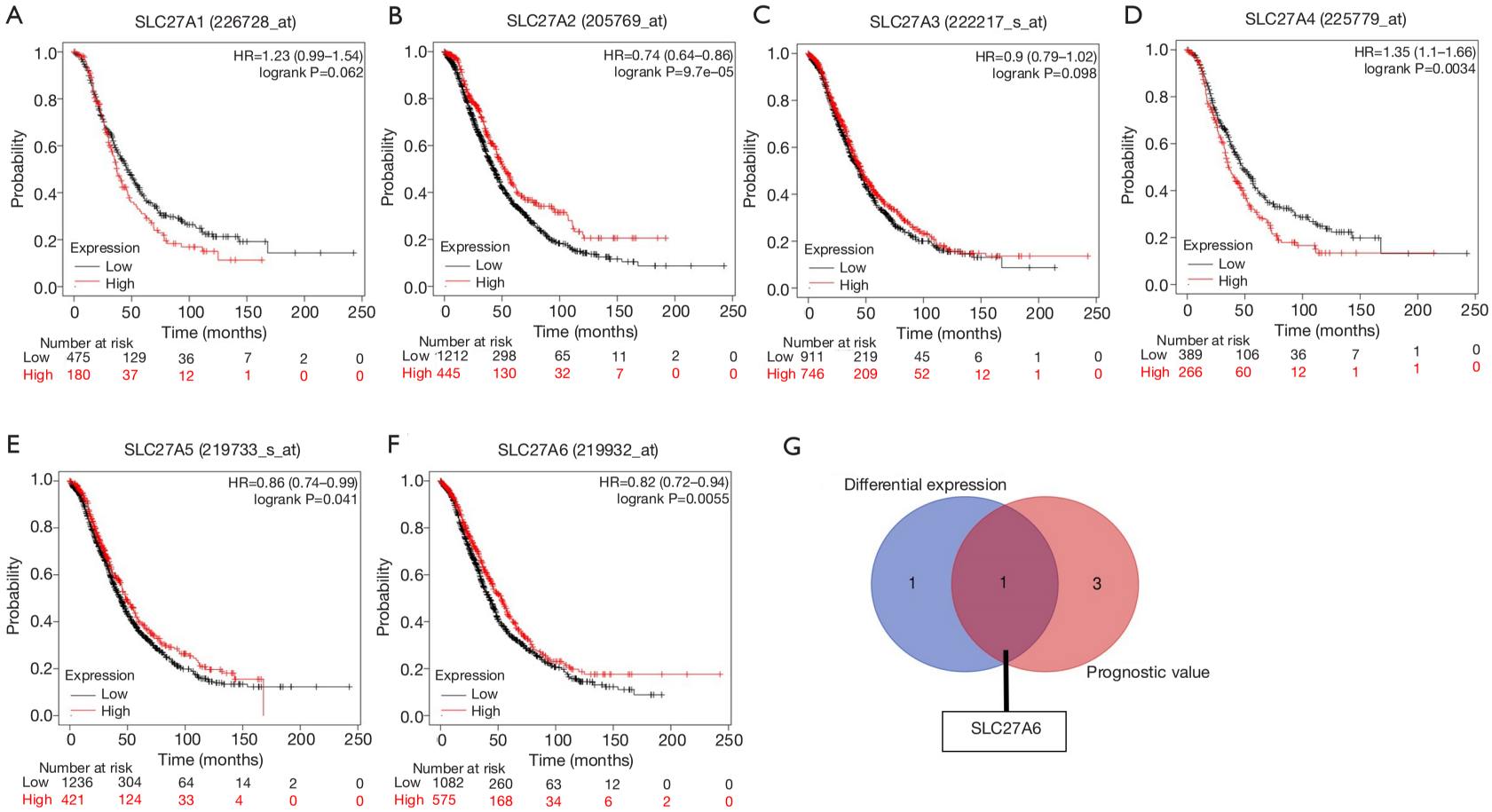

Figure 2 Prognostic value of SLC27As in patients with ovarian cancer based on the Kaplan-Meier plotter database. (A-F) Prognostic significance of individual SLC27As (*SLC27A1*, *SLC27A2*, *SLC27A3*, *SLC27A4*, *SLC27A5*, and *SLC27A6*) in ovarian cancer. (G) Venn diagram of differential expression and the prognostic value of the genes. SCL27As, solute-carrier family 27A molecules;

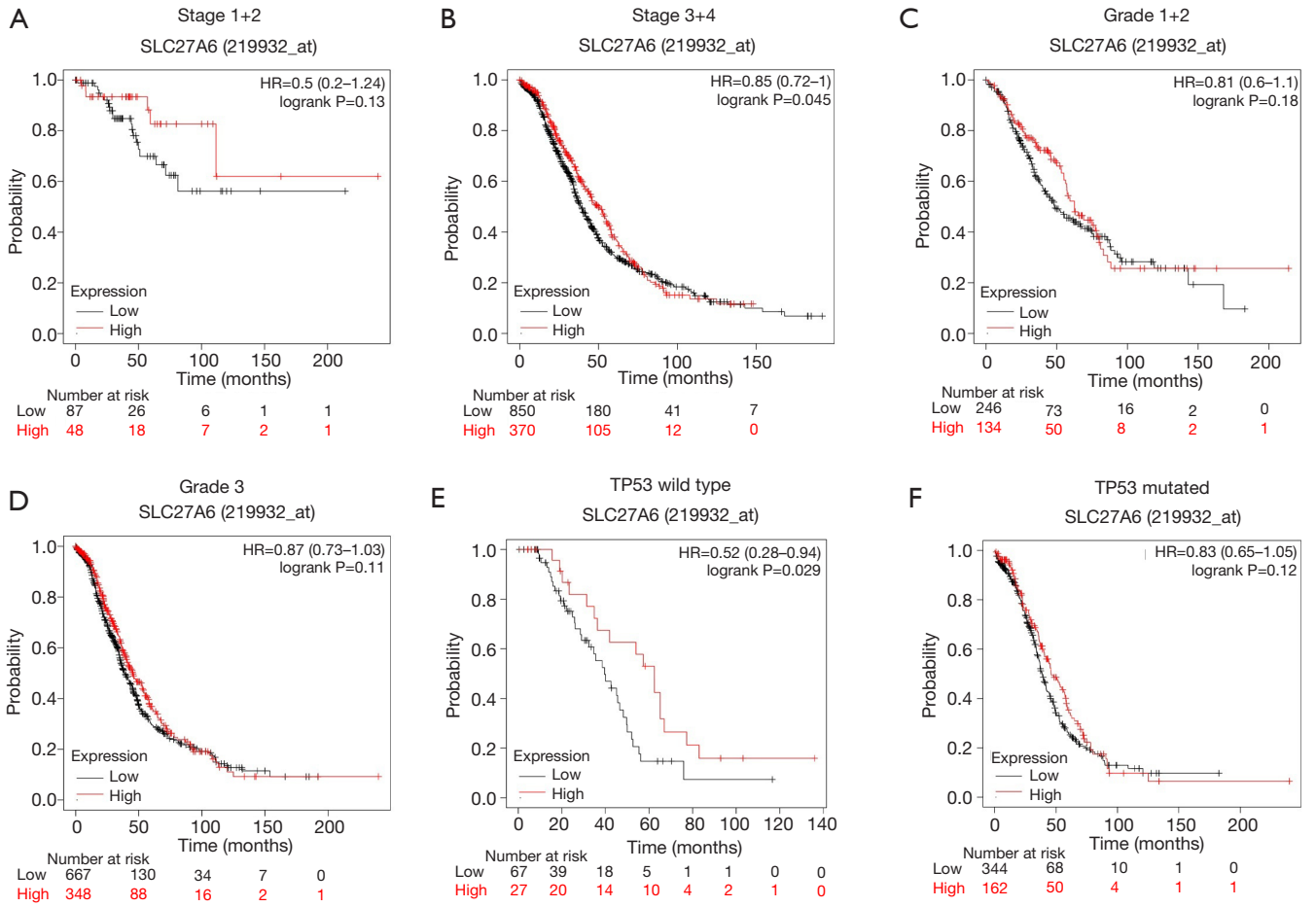

Figure 3 Prognostic value of *SLC27A6* in a subgroup of patients with ovarian cancer. Prognostic significance of *SLC27A6* expression in ovarian cancer patients with stage 1+2 (A), stage 3+4 (B), grade 1+2 (C), grade 3 (D), TP53 wild type (E), and TP53 mutated (F).

ovarian cancer database, of which 2,964 were significantly positively correlated (r>0.1, P<0.05) and 2,374 were significantly negatively correlated (r<–0.1, P<0.05). The volcano map and heat map are shown in *Figure 7A-7C*. Next, GO and KEGG enrichment analyses were used to explore the functions of genes related to SLC27A6. These genes are involved in BP (biological processes), such as homophilic cell adhesion via plasma membrane adhesion molecules, cell cycle G2/M phase transition, and stem cell differentiation. The genes in cellular component (CC) were involved in glutamatergic synapse, apical plasma membrane, and the apical part of the cell (*Figure 7D*). In addition, KEGG enrichment analysis (*Figure 7E*) showed that the pathways in which SLC27A6-related genes participated included the proteasome, cell cycle, Hippo signaling pathway, and so on.

The relationship between SLC27A6 expression and immune molecules in ovarian cancer

First, we checked the correlation between SLC27A6 expression and infiltrating immune cells. The infiltration levels of 28 immune cell types were obtained via single-sample gene set enrichment analysis (ssGSEA). We found that CD56dim natural killer (NK) cells, effector memory CD8 T cells, eosinophils, immature dendritic cells, mast cells, memory B cells, NK cells, T follicular helper cells, and type 2 T helper cells were significantly downregulated in the SLC27A6-low group compared with the SLC27A6-high group (*Figure 8A*). Next, the correlation between the expression of *SLC27A6* and immunomodulators was analyzed based on the Tumor and Immune System Interaction Database (TISIDB) (*Figure 8B*). The immunoinhibitors displaying the strongest

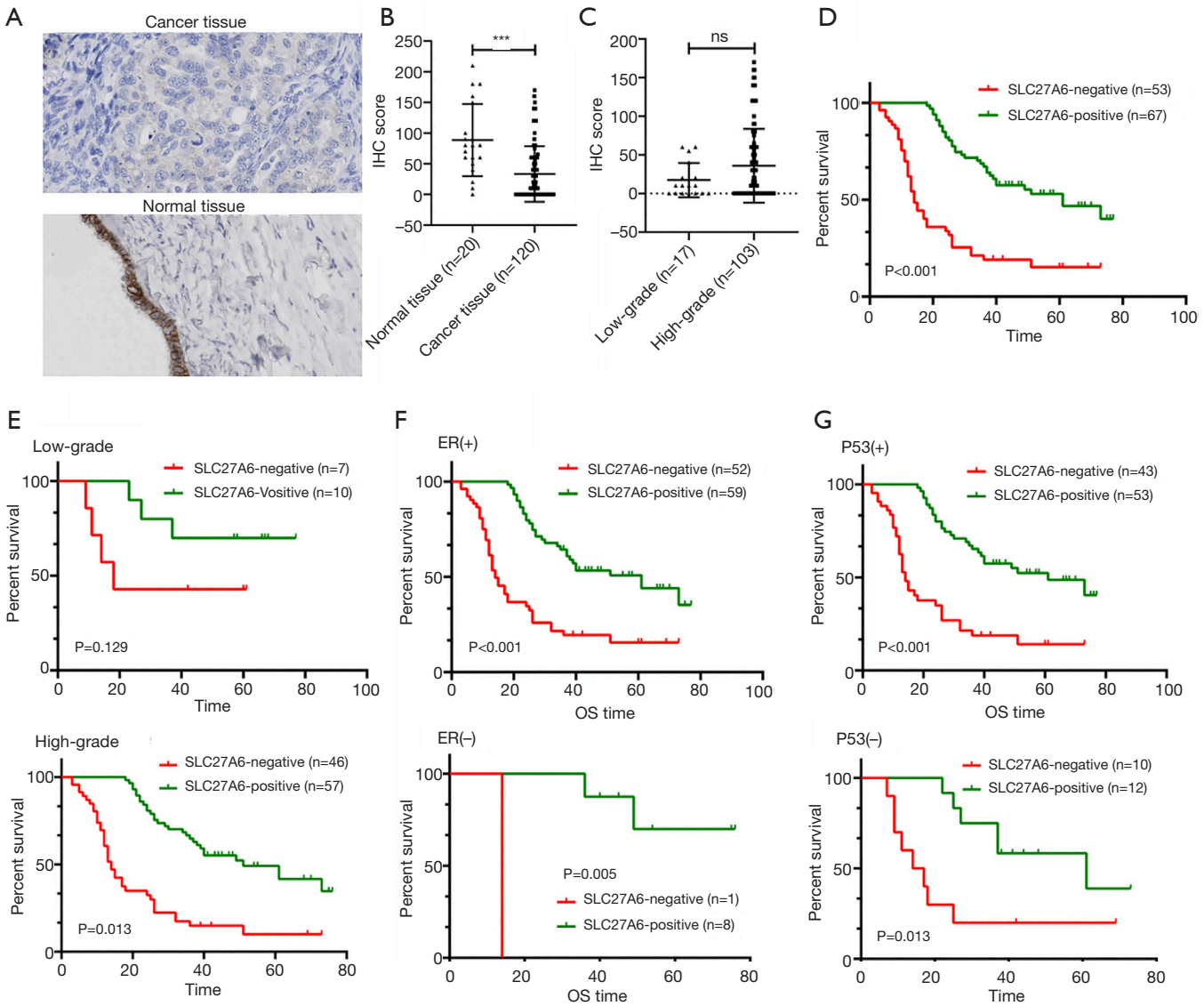

Figure 4 Validation of the protein expression and prognostic performance of *SLC27A6* in patients with ovarian cancer. (A) Representative images of *SLC27A6* staining using IHC in ovarian cancer tissue and normal tissue at ×200 magnification. (B) The IHC score of *SLC27A6* was significantly decreased in ovarian cancer tissues. (C) The IHC score of *SLC27A6* between low-grade ovarian cancer and high-grade ovarian cancer shows no significant difference. (D) Kaplan-Meier survival analysis and log-rank tests show that high expression levels of *SLC27A6* were associated with a poor prognosis (P=0.001). (E) Kaplan-Meier analysis of OS in high-grade or low-grade ovarian epithelial cancer patients. (F) Kaplan-Meier analysis of OS in ER(+) or ER(–) ovarian epithelial cancer patients. (G) Kaplan-Meier analysis of OS in TP53(+) or TP53(–) ovarian epithelial cancer patients. ***P<0.001. OS, overall survival; IHC, immunohistochemistry

correlation with *SLC27A6* expression included BTLA (r=0.138, P=0.0159) and IDO1 (r=0.14, P=0.0143). The immunostimulators displaying the strongest correlation with SLC27A6 expression included IL6R (r=0.234, P=3.73e–05), TMEM173 (r=0.305, P=5.56e–08), TNFRSF13C (r=–0.261, P=3.94e–04), and TNFSF14 (r=0.223, P=8.45e–05). The major histocompatibility complex (MHC) molecules displaying the strongest correlation with *SLC27A6* expression included HLA-DMA (r=0.119, P=0.0365), HLA-DOA (r=0.157, P=0.00592), HLA-DOB (r=0.13, P=0.0223),

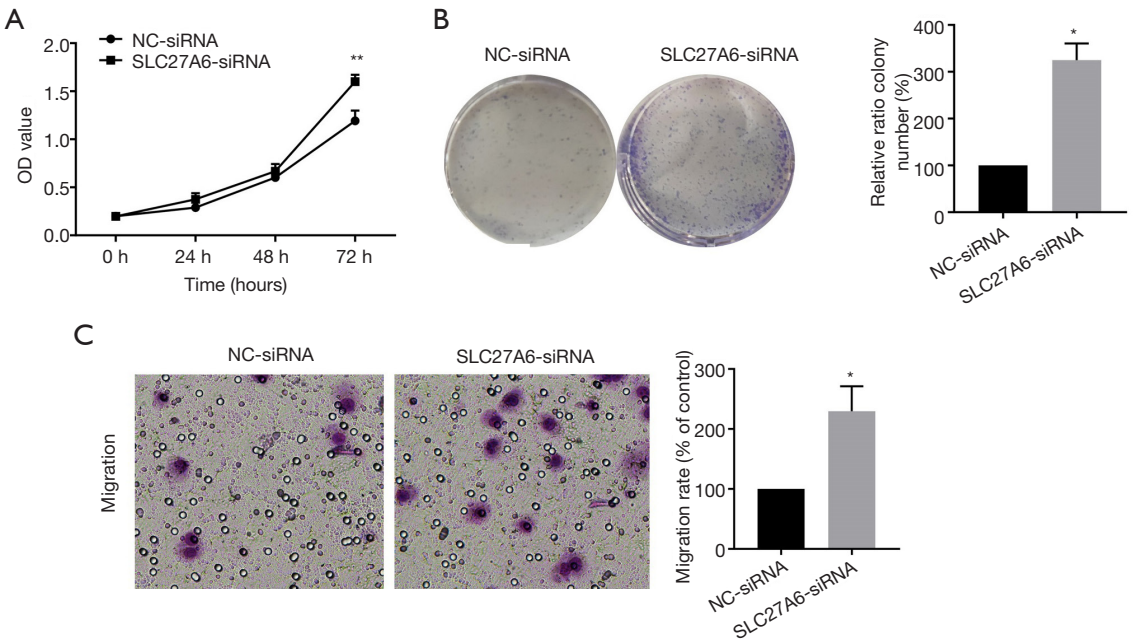

Figure 5 Functional validation of *SLC27A6* in A2780 ovarian cancer cells. A2780 cells were transfected with NC-siRNA or SLC27A6-siRNA. CCK-8 assays (A), colony formation assays (B), and Transwell assays (C) were performed (stained with crystal violet and counted under a light microscope at ×400 magnification). *P<0.05; **P<0.01. CCK-8, Cell Counting Kit-8; NC-siRNA, negative control small interfering RNA.

and TAPBP (r=0.115, P=0.0447).

Discussion

Due to the lack of early screening markers and preventive tests, 70% of ovarian cancer patients are already in the advanced stage at the time of diagnosis, leading to ovarian cancer being the main cause of death among all gynecological tumors (24,25). Lipid metabolism reprogramming plays an important role in the occurrence and development of ovarian cancer. In addition, lipidomic analysis of serum samples indicated that there are significant differences in lipid molecules between ovarian cancer patients and normal controls (26). Finally, targeted lipid metabolism signaling pathways have shown great clinical application prospects in preventing peritoneal metastasis of ovarian cancer (14). Overall, in-depth exploration of the expression and clinical significance of lipid metabolism molecules is of great significance for improving the prognosis of patients with ovarian cancer.

The SCL27As play an important role in lipid metabolism by regulating the uptake of long-chain fatty acids (27,28), which can affect the occurrence and development of a variety of malignant tumors. However, the roles of *SCL27A* family members (SCL27A1-6) in ovarian cancer are still unknown. In our study, we analyzed the expression and prognostic value of SCL27A family members (SCL27A1-6) in ovarian cancer tissues. Compared with normal ovarian tissues, *SLC27A1* and *SLC27A6* are expressed at low levels in ovarian cancer tissues. Prognostic analysis showed that *SLC27A2*, *SLC27A5*, and *SLC27A6* are protective factors for patients with ovarian cancer, and *SLC27A4* can be used to predict a poor prognosis of these patients. These results indicate that SCL27As play a crucial role in the progression of ovarian cancer; however, their functions and molecular mechanisms need to be further elucidated.

We selected SLC27A6 for subsequent analysis because it had both significant differential expression and good prognostic value. Early research showed that *SLC27A6* is primarily expressed in the heart and seems to be involved in cardiac fatty acid uptake. A variant in *SLC27A6* is associated with lower fasting and postprandial triacylglycerol (TAG), low blood pressure, and left ventricular hypertrophy (29). A study in breast cancer has shown that the expression level of *SLC27A6* in breast cancer tissues and breast cancer cells is significantly lower than that in normal breast tissues and

Figure 6 Genetic variations of *SLC27A6* in ovarian cancer based on cBioPortal. (A) Genetic variations in the *SLC27A6* gene reported in different studies. (B) OncoPrint overview of the genetic variations in the *SLC27A6* gene.

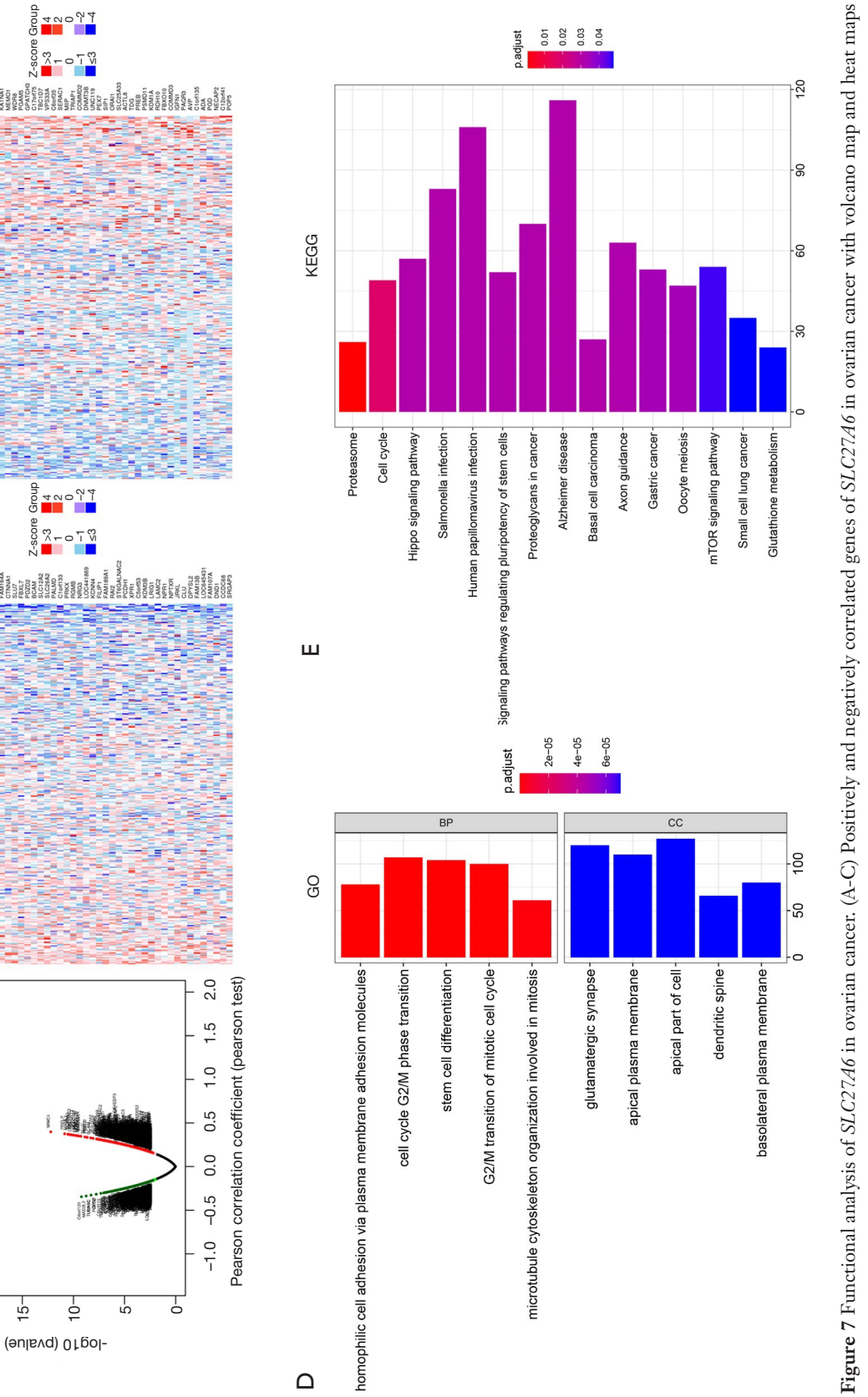

Figure 7 Functional analysis of *SLC27A6* in ovarian cancer. (A-C) Positively and negatively correlated genes of *SLC27A6* in ovarian cancer with volcano map and heat maps (TOP 50). (D) Results of GO analysis. (E) Results of KEGG analysis. GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.

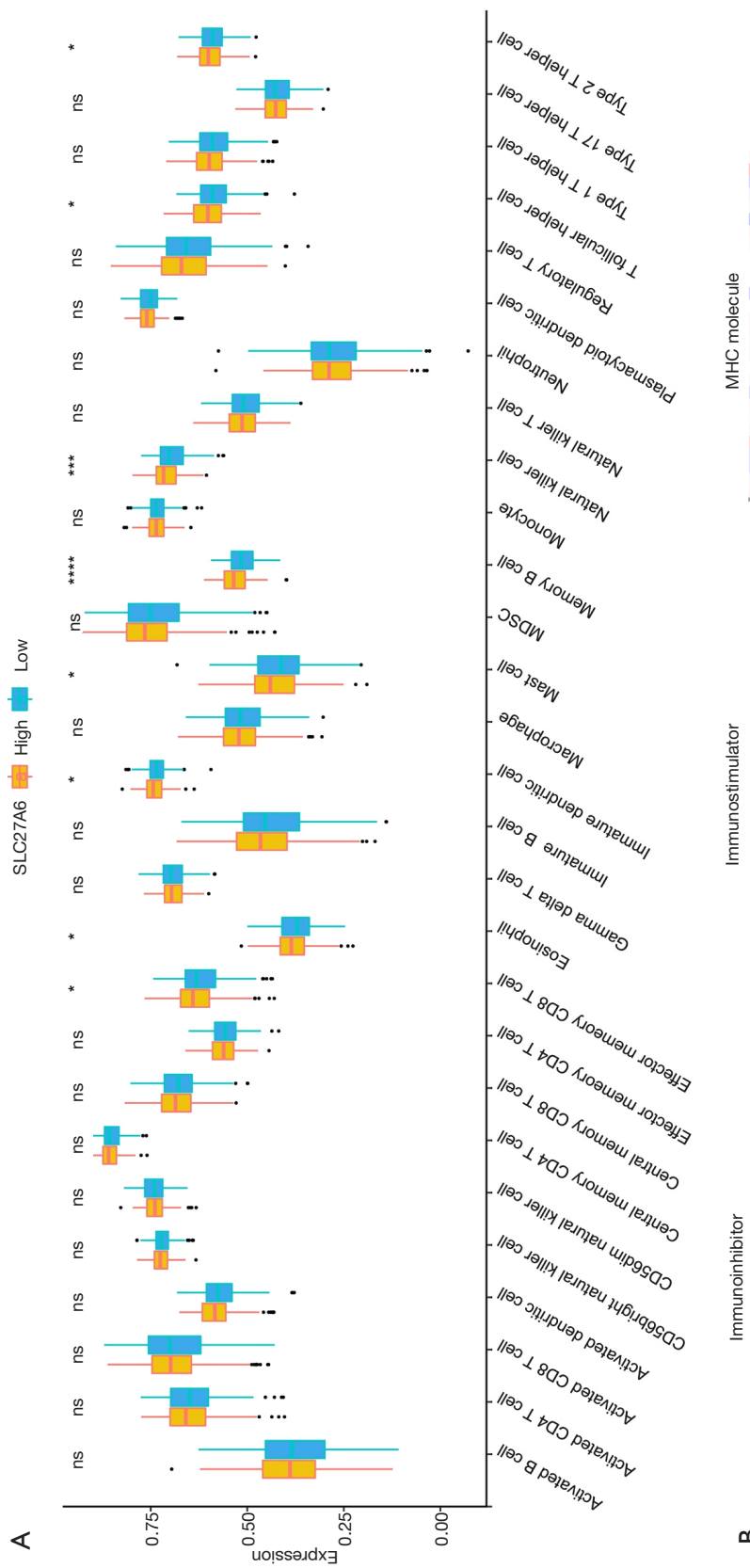

Figure 8 The correlation between *SLC27A6* expression and infiltrating immune cells and the correlation between *SLC27A6* expression and immunomodulators. (A) Distribution level of 28 types of immune cells in the *SLC27A6*-high group and *SLC27A6*-low group. (B) The abundances of immunoinhibitors, immunostimulators, and MHCs correlated with *SLC27A6* expression. *P<0.05, ***P<0.001 and ****P<0.0001.

breast cells (30). In addition, *SLC27A6* was confirmed to be related to enzalutamide resistance in prostate cancer (31). However, the clinical value of *SLC27A6* in ovarian cancer is unclear.

In this study, we confirmed the clinical value of *SLC27A* in ovarian cancer based on clinical samples. And our *in vitro* experiment results showed that knocking down the expression of *SLC27A6* could significantly enhance the malignant biological behavior of ovarian cancer cells. In conclusion, we confirmed that *SLC27A6* is a potential tumor suppressor gene in ovarian cancer. In addition, via bioinformatics, we analyzed the genetic variations of *SLC27A6*, which indicated that *SLC27A6* had a high mutation frequency in malignant tumors. We found that *SLC27A6* may affect the occurrence and development of tumor cells by participating in proteasome, cell cycle, Hippo signaling pathway, and *SLC27A6* may participate in tumor immune response by regulating the activity (or number) of immune cells. We also found the immunosuppressants, immunomodulators, and MHC molecules that may be related to *SLC27A6*, which need further verification based on *in vivo* and *in vitro* experiments. Such experiments will be performed and reported on in future.

Overall, this study revealed the abnormal expression and prognostic value of SLC27As in ovarian cancer. Notably, *SLC27A6* may be a novel biomarker for the diagnosis and prognostication of ovarian cancer patients.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional/regional/national ethics/committee/ethics board of the the First Affiliated hospital of China Medical University (No.: AF-SOP-07-1.1-01) and informed consent was taken from all the patients.

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