Original Article

The mitosis-related gene *OIP5* is a potential biomarker in pan-cancer

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Background: *OIP5* is found at the centromere and plays an important role in recruiting centromere protein-A (CENP-A) through interacting with Holliday junction recognition protein during cell mitosis. *OIP5* is considered to be a cancer-testis specific gene, but its function in tumor development remains unclear. Increased expression of *OIP5* has been reported in testis as well as in different cancers; however, the underlying mechanisms remain obscure.

Methods: Data were collected from the Genotype-Tissue Expression project, the Cancer Cell Line Encyclopedia, and The Cancer Genome Atlas (TCGA) to analyze the effect of *OIP5* in many common cancers. Analyses of the differential expression of *OIP5* and its relationships with prognosis, the tumor microenvironment, immune infiltration, immune regulation, neoantigen production, and genomic stability in various cancers were performed using R software.

Results: Expression of *OIP5* was significantly increased in 34 common tumor types compared with matched healthy samples; however, no significant increases were observed in pheochromocytoma and paraganglioma or kidney chromophobe. Elevated *OIP5* expression predicted dismal overall survival in 14 tumors. The function of *OIP5* in tumor-infiltrating immune cells (TIIC) was analyzed, and *OIP5* might inhibit TIIC infiltration in the tumor microenvironment; a positive correlation was found in thymoma, while a negative correlation was observed in lung squamous cell carcinoma and lung adenocarcinoma. High *OIP5* expression was related to immune regulation and neoantigen production, particularly in terms of the levels of immune regulatory molecules and the number of neoantigens produced in lung adenocarcinoma, uterine corpus endometrial carcinoma, breast cancer, stomach adenocarcinoma, low-grade glioma, and prostate adenocarcinoma. It was also associated with increased cell genome instability in lung adenocarcinoma. Gene set enrichment analysis revealed potential critical effects of *OIP5* on the cell cycle, base excision repair, homologous recombination, DNA replication, the p53 signaling pathway, and mismatch repair pathways.

Conclusions: High expression of *OIP5* is found in many common tumors and predicts a dismal prognostic outcome. The gene is an important recruitment factor for CENP-A and may promote tumor progression by affecting the tumor immune microenvironment and genomic stability. Therefore, *OIP5* can serve as a potential candidate factor to predict cancer prognosis and guide the use of therapeutics.

Keywords: *OIP5*; mitosis; pan-cancer analysis

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Introduction

Malignant tumors are major causes of mortality globally, and research to uncover the related molecular mechanisms has been conducted worldwide (1). Cancers have a genetic component with a common complex molecular process; therefore, exploration of the homogeneity of a particular gene across various tumors is crucial to discovering new clinical therapeutic targets and prognostic evaluation signs (2). Recently, immune checkpoint blockade therapies have been developed, and through the use of public databases such as The Cancer Genome Atlas (TCGA), scientists have continued to improve and search for new immunotherapeutic targets by analyzing pan-oncogene levels and assessing their relationship with prognostic outcomes and related signaling pathways (3,4). Therefore, it is necessary to analyze pan-cancer gene expression levels, evaluate their relationship with prognostic outcomes, and understand their molecular mechanism to identify novel therapeutics.

OIP5 is located on human chromosome 15 and encodes a 25-kDa protein with one coiled-coil domain. It was identified through a yeast two-hybrid test and was found to interact with Opa (Neisseria gonorrhoeae opacity-associated) proteins (5). *OIP5* is found at the centromere and plays an important role in recruiting centromere protein-A (CENP-A) through interacting with the Holliday junction recognition protein (6). CENP-A, which contributes to chromosome fragility in human cancer, is overexpressed and localized abnormally in many kinds of cancers (7). Increased expression of *OIP5* also has been reported in testis as well as a diverse range of cancers, such as glioblastoma, bladder cancer (BLCA), oral cancer, and lung cancer, and it has been associated with different tumor biological events (8-11). As a result, *OIP5* is considered to be a cancer-testis specific gene, but its function in tumor development remains unclear (12). Therefore, a pan-cancer analysis is required to investigate its potential function as a novel target for tumor treatment.

In this study, we analyzed *OIP5* expression levels within a diverse range of cancers and their association with prognosis using data from the Genotype-Tissue Expression (GTEx) project, TCGA, and the Cancer Cell Line Encyclopedia (CCLE). Further, to understand the impact of *OIP5* on the immune microenvironment and malignant progression of tumors, we examined the relationships of *OIP5* expression with immunomodulation, tumor-infiltrating immune cells (TIICs), microsatellite instability (MSI), tumor mutational burden (TMB), mRNA expression-based stemness score (RNAss), and DNA methylation-based stemness score (DNAss) in various cancers. To investigate the role of *OIP5* in cancer in more detail, we also carried out gene set enrichment analysis (GSEA). We present the following article in accordance with the REMARK reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-6640/rc).

Highlight box

Key findings
- *OIP5* plays a role in promoting cancer in many types of tumors.

What is known and what is new?
- *OIP5* is a key molecule in mitosis and is increased in testis and different cancers.
- *OIP5* may promote tumor progression by affecting the tumor immune microenvironment and genomic stability.

What is the implication, and what should change now?
- *OIP5* can serve as a potential candidate factor to predict prognosis and guide the use of therapeutics in cancer.

Methods

Data acquisition

Data on *OIP5* expression levels in diverse cancers and matched healthy samples were acquired from the GTEx (https://commonfund.nih.gov/GTEx/), CCLE (https://portals.broadinstitute.org), and TCGA (http://cancergenome.nih.gov/) databases (13). The Tumor IMmune Estimation Resource dataset (TIMER, http://timer.cistrome.org/) was used for comprehensive assessment

of the abundance of TIICs (14). Gene somatic mutation data were also downloaded for analysis. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Gene expression levels

The expression levels of *OIP5* in 31 healthy samples and 21 diverse tumor samples were compared using the Kruskal-Wallis test. After that, using TCGA data, *OIP5* expression in tumor tissues was compared with that in corresponding healthy tissues. Due to the insufficient number of healthy noncancerous samples available from the TCGA database, healthy control sample data were also collected from the GTEx database.

Survival prognosis analysis

Clinical phenotypic and survival information of TCGA cases was extracted. Univariate regression was used to assess the relationships of *OIP5* with the following four prognostic indicators in different tumors: overall survival (OS), disease-specific survival (DSS), disease-free survival (DFS), and progression-free survival (PFS). Cases were classified into the high- or low-expression group based on the median *OIP5* level. The Kaplan-Meier method and log-rank test were used for the survival analysis of each cancer.

Analysis of the effect of OIP5 on TIICs and the tumor microenvironment

The effect of *OIP5* on TIIC infiltration levels in diverse cancers was assessed using Spearman's rank correlation coefficient. The TIICs of focus mainly included $CD4^+$ T cells, $CD8^+$ T cells, B cells, dendritic cells, macrophages, and neutrophils. The Estimation of STromal and Immune cells in MAlignant Tumors using Expression data (ESTIMATE) algorithm was used to determine the immune, stromal, and ESTIMATE scores of different samples, and the relationships between *OIP5* expression levels with these scores were also assessed (15).

Analysis of the correlations of OIP5 expression with immunomodulation, immune neoantigens, and gene mutations

The correlations of *OIP5* expression level with 150 common immune-related molecules, including the major histocompatibility complex, chemokines, chemokine receptors, immune stimulator proteins, and immune inhibitors, were analyzed using Spearman's rank correlation coefficient. Similarly, the relationship between *OIP5* expression level and the number of neoantigens was evaluated for each tumor type. The gene mutation information of 514 cases with lung adenocarcinoma (LUAD) was retrieved from the TCGA database; the samples were classified and compared based on *OIP5* expression, and the role of *OIP5* in cell genome stability was evaluated.

Analysis of the correlations of OIP5 expression with DNAss, RNAss, TMB, and MSI

The correlations of *OIP5* expression level with the DNAss, RNAss, TMB, and MSI were examined in different tumors by calculating the Pearson's correlation coefficient.

GSEA

To identify significantly different pathways in the high and low *OIP5* expression groups, GSEA was performed. The Kyoto Encyclopedia of Genes and Genomes (https://www.kegg.jp.) database was used for analysis. The criteria for significance were set at normalized enrichment score (NES) >1.5, false discovery rate (FDR) <0.25, and P value <0.05.

Statistical analysis

The R software (version 4.0.2; https://www.R-project.org) was used for data analysis, and plots were obtained using various R packages, including limma (16), clusterprofiler (17), survival (18), and ggplot2 (19). P value <0.05 was considered to be statistically significant.

Results

OIP5 showed up-regulation in various malignancies

Levels of *OIP5* expression were analyzed in cancer and healthy samples from the GTEx, TCGA, and CCLE databases. In the GTEx dataset analysis, *OIP5* expression was found in 31 healthy samples, with high expression in the testis and bone marrow and low expression in the heart and pancreas (*Figure 1A*). Based on CCLE data, *OIP5* expression was highest in hematopoietic and lymphoid tissue and lowest in the kidney (*Figure 1B*). *OIP5* expression levels were analyzed in samples and matched non-

carcinoma samples derived from the TCGA (*Figure 1C*) in combination with normal tissue data from the GTEx project (*Figure 1D*). Compared to normal tissues, all solid tumors showed increased expression of *OIP5* except for pheochromocytoma and paraganglioma and kidney chromophobe (KICH).

Prognostic significance of OIP5 in pan-cancer

To evaluate the prognostic role of *OIP5* in different cancers, we next conducted univariate Cox regression. Results showed that *OIP5* expression predicted poor OS in adrenocortical carcinoma (ACC), LUAD, the pan-kidney cohort [KICH, kidney renal clear cell carcinoma (KIRC), and kidney renal papillary cell carcinoma (KIRP)], glioblastoma multiforme low-grade glioma (LGG), and many other cancers (*Figure 2A*). Similar results were observed for DSS (*Figure 2B*), DFS (*Figure 2C*), and PFS (*Figure 2D*).

Further, Kaplan-Meier curves were plotted to analyze OS, DSS, DFS, and PFS in patients with cancer based on *OIP5* expression. Increased expression of *OIP5* was found to predict dismal OS in ACC, BLCA, KICH, KIRC, KIRP, LGG, liver hepatocellular carcinoma (LIHC), LUAD, mesothelioma (MESO), pancreatic adenocarcinoma (PAAD), prostate adenocarcinoma (PRAD), thymoma (THYM), and uveal melanoma (UVM). Interestingly, in contrast, *OIP5* expression was associated with longer OS in THYM (*Figure 3*). To eliminate the effect of death from non-cancer causes on the statistical results, DSS was used as the end event. The results confirmed that increased *OIP5* expression had similar prognostic significance for DSS as it did for OS in all tumors, except THYM (*Figure 4*). Increased expression of *OIP5* predicted dismal prognostic outcomes in ACC, breast cancer (BRCA), KIRP, LIHC, PAAD, and PRAD, as revealed by DFS analysis (*Figure 5*). Results also showed that *OIP5* expression was similarly correlated with PFS (*Figure 6*). See Table S1 for a full list of abbreviations used.

Effects of OIP5 on tumor immune infiltration and the tumor immune microenvironment

The effect of *OIP5* expression on TIIC recruitment was investigated through analysis of the relationship of *OIP5* gene expression levels with the numbers of $CD4^+$ T cells, $CD8^+$ T cells, B cells, dendritic cells, neutrophils, and macrophages in different tumors. *OIP5* expression was negatively related to TIIC levels in LUAD, lung squamous cell carcinoma (LUSC), esophageal carcinoma, and stomach and esophageal carcinoma. However, a positive relationship was found between TIIC levels and increased expression of *OIP5* in THYM, thyroid carcinoma, KIRC, and LGG (*Figure 7A*).

We also analyzed the effect of *OIP5* on the tumor microenvironment by assessing the relationships of *OIP5* gene expression level with the stromal score, immune score, and ESTIMATE score. *OIP5* expression showed negative relationships with stromal score (*Figure 7B*), immune score (*Figure 7C*), and ESTIMATE score (*Figure 7D*) in LUAD, stomach and esophageal carcinoma, stomach adenocarcinoma (STAD), and LUSC. These results suggested that *OIP5* might inhibit TIIC infiltration in the tumor microenvironment.

Correlation analysis of OIP5 expression levels with immune regulation, neoantigens, and gene mutation

Based on the effect of *OIP5* expression on the immune microenvironment, we further examined the association between *OIP5* expression and 150 common immunomodulatory molecules in 40 different tumors. Surprisingly, *OIP5* showed a negative correlation with the levels of most immunomodulators in LUAD, LUSC, and STAD but showed a positive correlation with immunomodulator levels in thyroid carcinoma, the pan-kidney cohort, breast cancer, ovarian cancer, and other tumors (*Figure 8A*). This result suggested that *OIP5* possibly affects TIIC levels by regulating the specific immune response.

Additionally, we also analyzed the association between the number of neoantigens and *OIP5* expression in each cancer. *OIP5* expression showed a positive correlation with neoantigen number in LUAD, uterine corpus endometrial carcinoma, breast cancer, STAD, low-grade glioma, and prostate adenocarcinoma (*Figure 8B*). These findings suggested that *OIP5* possibly enhances neoantigen generation in cancer cells, which was further confirmed by gene mutation analysis. In LUAD, more gene mutations were observed in the *OIP5* high-expression group than in the low-expression group. In particular, *TP53*, which is a well-known tumor suppressor gene, had a remarkably

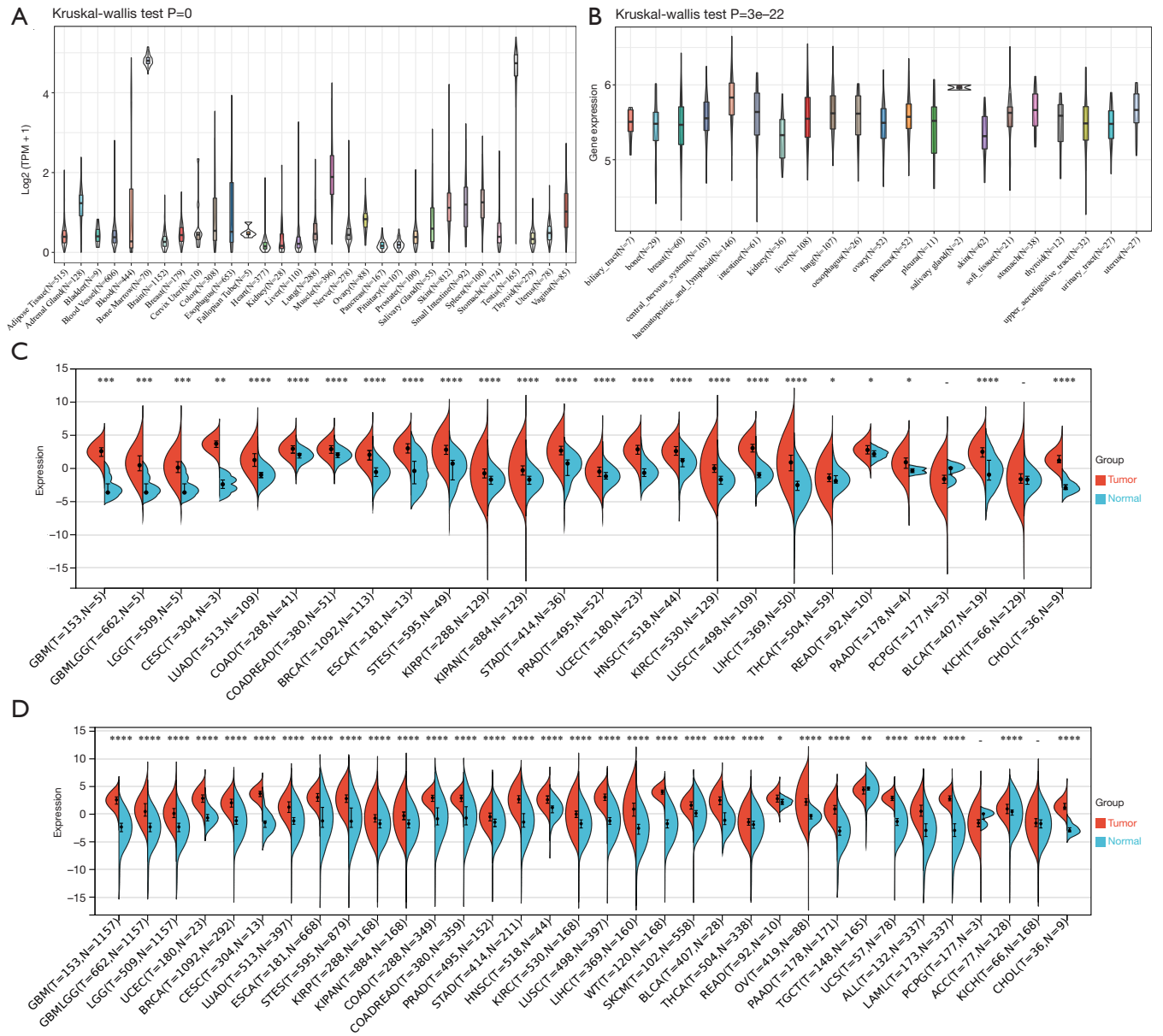

Figure 1 Expression analysis of *OIP5* in pan-cancer. (A) Analysis of *OIP5* expression levels in 31 different normal tissue types with data from the GTEx project. (B) Analysis of *OIP5* expression levels in cell lines of 21 different tumors with data from the CCLE dataset. (C) Analysis of *OIP5* expression levels in 26 types of matched tumor and normal tissues with data from the TCGA database. (D) Analysis of *OIP5* expression levels in 34 types of matched tumor tissues from the TCGA database and normal tissues from the GTEx project database. *, P<0.05; **, P<0.01; ***, P<0.001; ****, P<0.0001. TCGA, The Cancer Genome Atlas; GTEx, the Genotype-Tissue Expression.

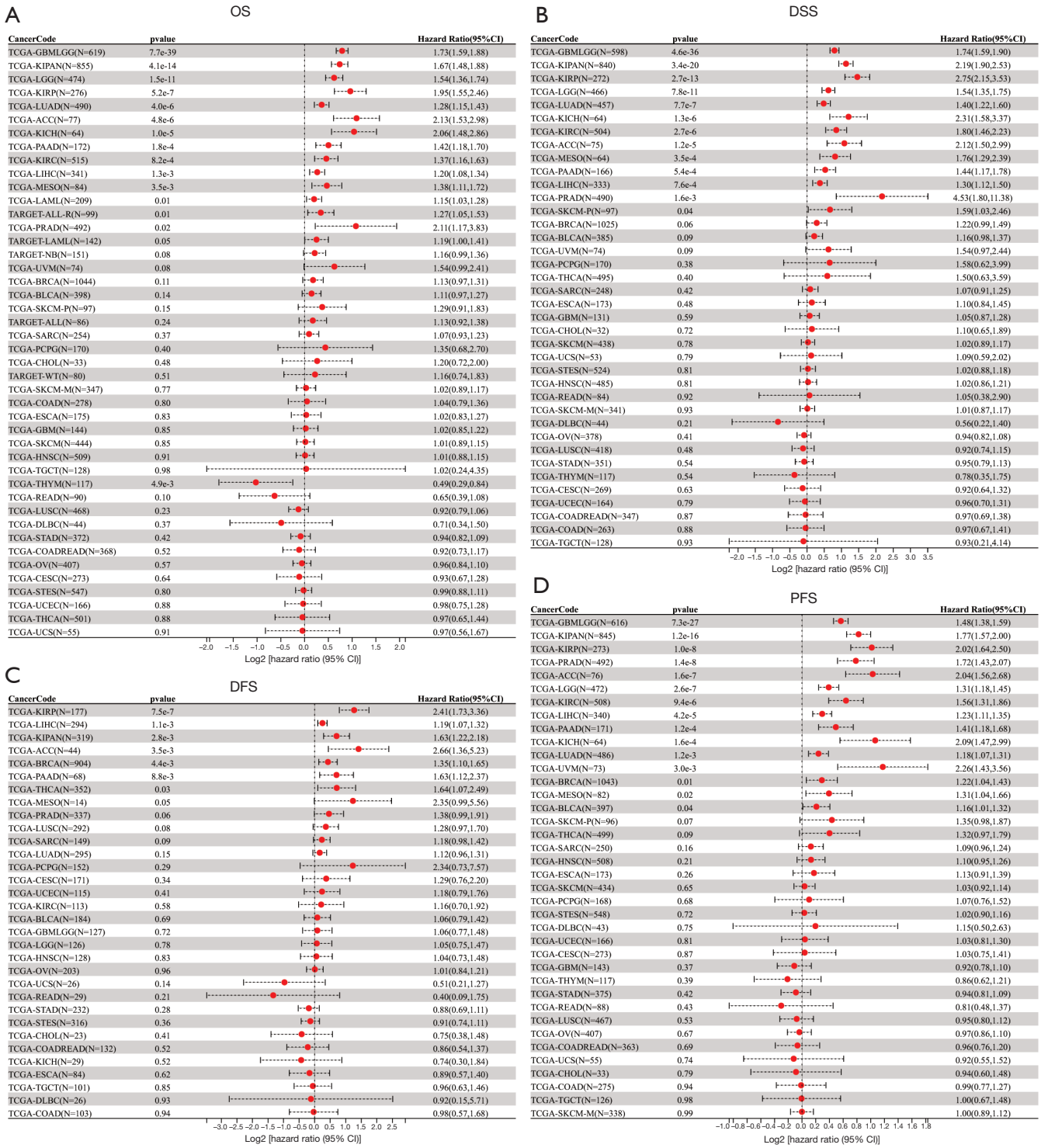

Figure 2 Forest plot of associations between *OIP5* expression and overall, disease-specific, disease-free, and progression-free survival. Association of *OIP5* with (A) OS, (B) DSS, (C) DFS, and (D) PFS. OS, overall survival; DSS, disease-specific survival; DFS, disease-free survival; PFS, progression-free survival.

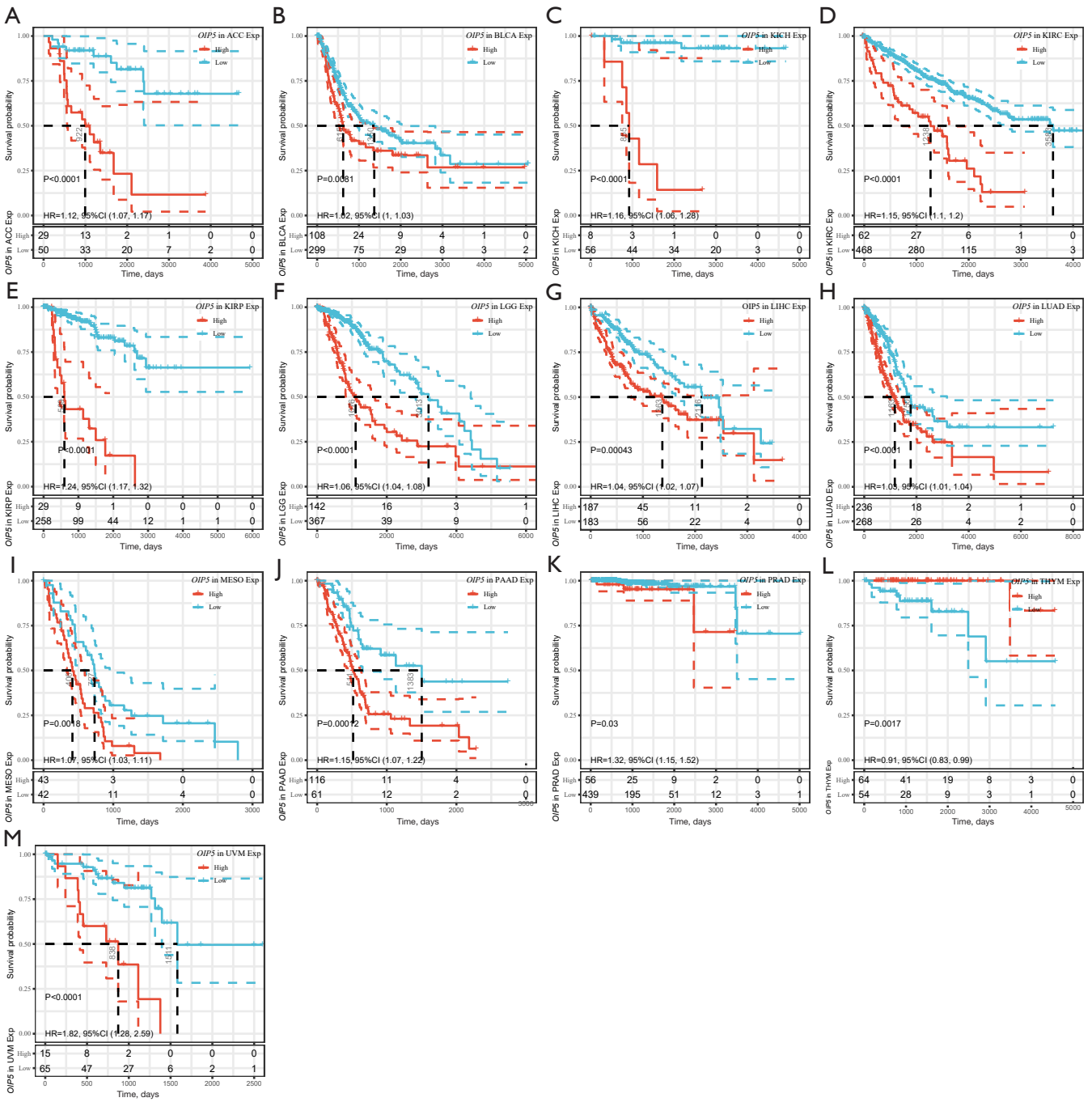

Figure 3 Kaplan-Meier analysis of overall survival according to *OIP5* expression level in different tumors. (A) ACC, (B) BLCA, (C) KICH, (D) KIRC, (E) KIRP, (F) LGG, (G) LIHC, (H) LUAD, (I) MESO, (J) PAAD, (K) PRAD, (L) THYM, and (M) UVM.

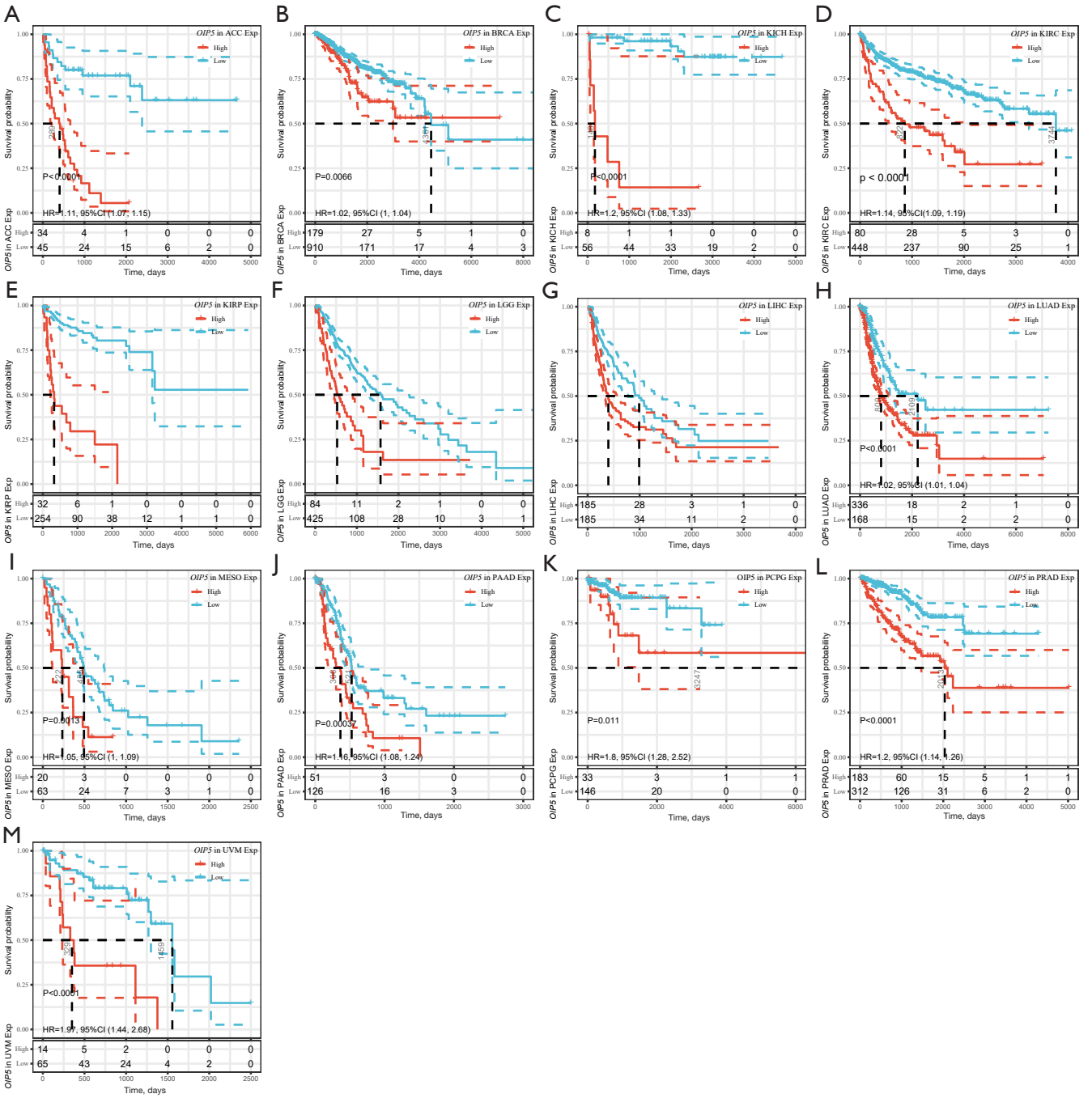

Figure 4 Kaplan-Meier analysis of disease-specific survival according to *OIP5* expression level in different tumors. (A) (A) ACC, (B) BRCA, (C) KICH, (D) KIRC, (E) KIRP, (F) LGG, (G) LIHC, (H) LUAD, (I) MESO, (J) PAAD, (K)PCPG, (L) PRAD, and (M) UVM.

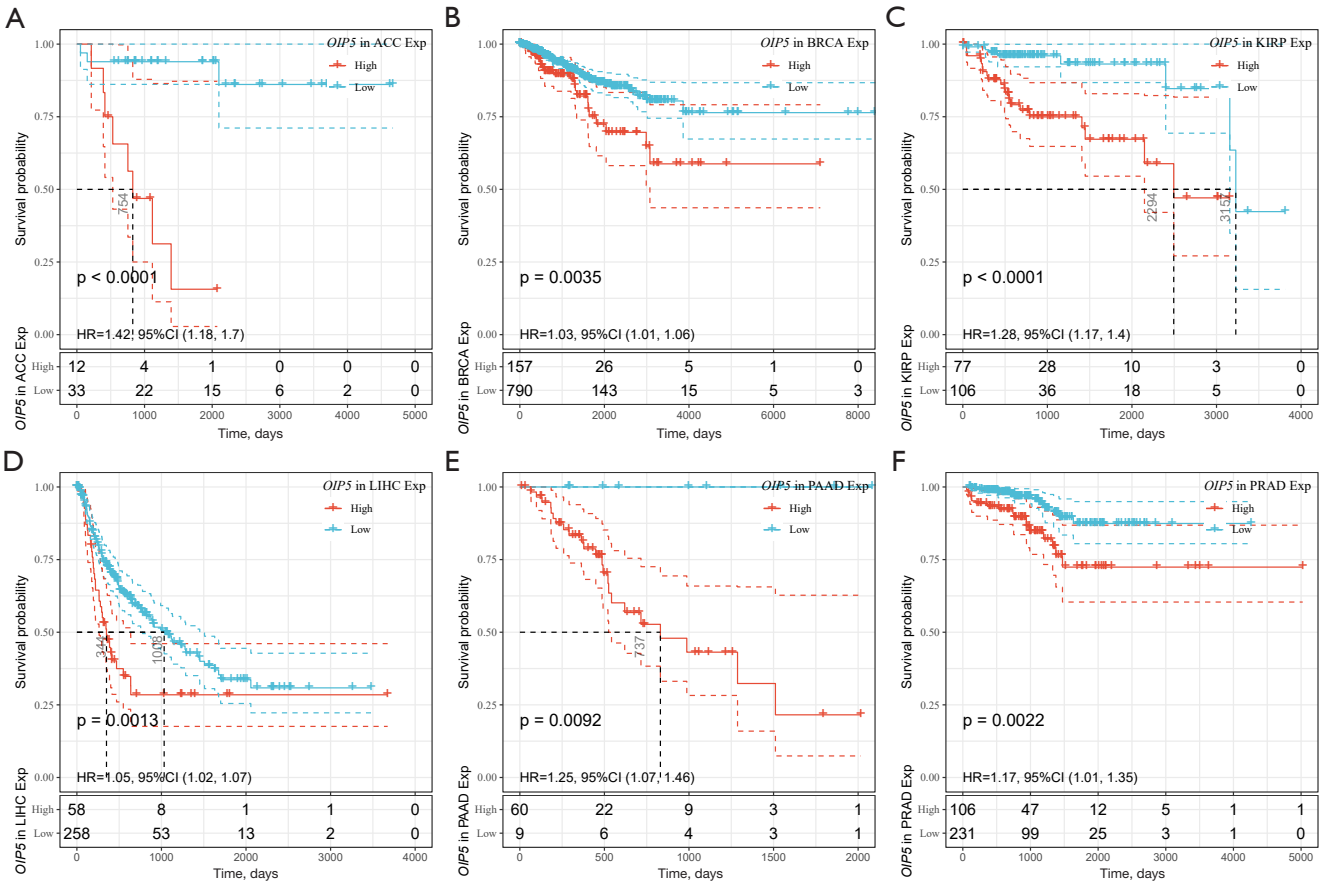

Figure 5 Kaplan-Meier analysis of disease-free survival according to *OIP5* expression level in different tumors. (A) ACC, (B) BRCA, (C) KIRP, (D) LIHC, (E) PAAD, and (F) PRAD.

increased mutation rate (*Figure 8C*).

Association of OIP5 expression level with DNAss, RNAss, TMB, and MSI

The DNAss and RNAss of tumor cells have been reported to be tightly associated with tumor progression, metastasis, and drug resistance (20). MSI and TMB are indicators of tumor cell genomic stability (21).

In this study, *OIP5* expression showed a positive relationship with both the DNAss (*Figure 9A*) and RNAss (*Figure 9B*) in many tumors, including LUAD, LUSC, STAD, and testicular germ cell tumors. The *OIP5* expression level also showed a positive correlation with TMB in many tumors, such as LUAD, STAD, and KICH, but a negative correlation with THYM, ovarian cancer, and thyroid carcinoma (*Figure 9C*). Moreover, the expression of *OIP5* was positively correlated with MSI in STAD, cholangiocarcinoma, and stomach and esophageal carcinoma but was negatively correlated with MSI in glioblastoma multiforme low-grade glioma and testicular germ cell tumors (*Figure 9D*).

GSEA

The protein-protein interaction network of *OIP5* was generated to understand the function and potential mechanism of *OIP5* in cells. Surprisingly, the results showed that *OIP5* was linked to CENP-A, CENP-M, CENPN, CENP-U, MIS18A, MIS18BP1, HJURP, NCAPG, NUSAP1, and CDCA8, which are all mitosis-related proteins (*Figure 10A*). Furthermore, to evaluate the possible biological involvement of *OIP5* using GSEA analysis, data in The Kyoto Encyclopedia of Genes and Genomes were

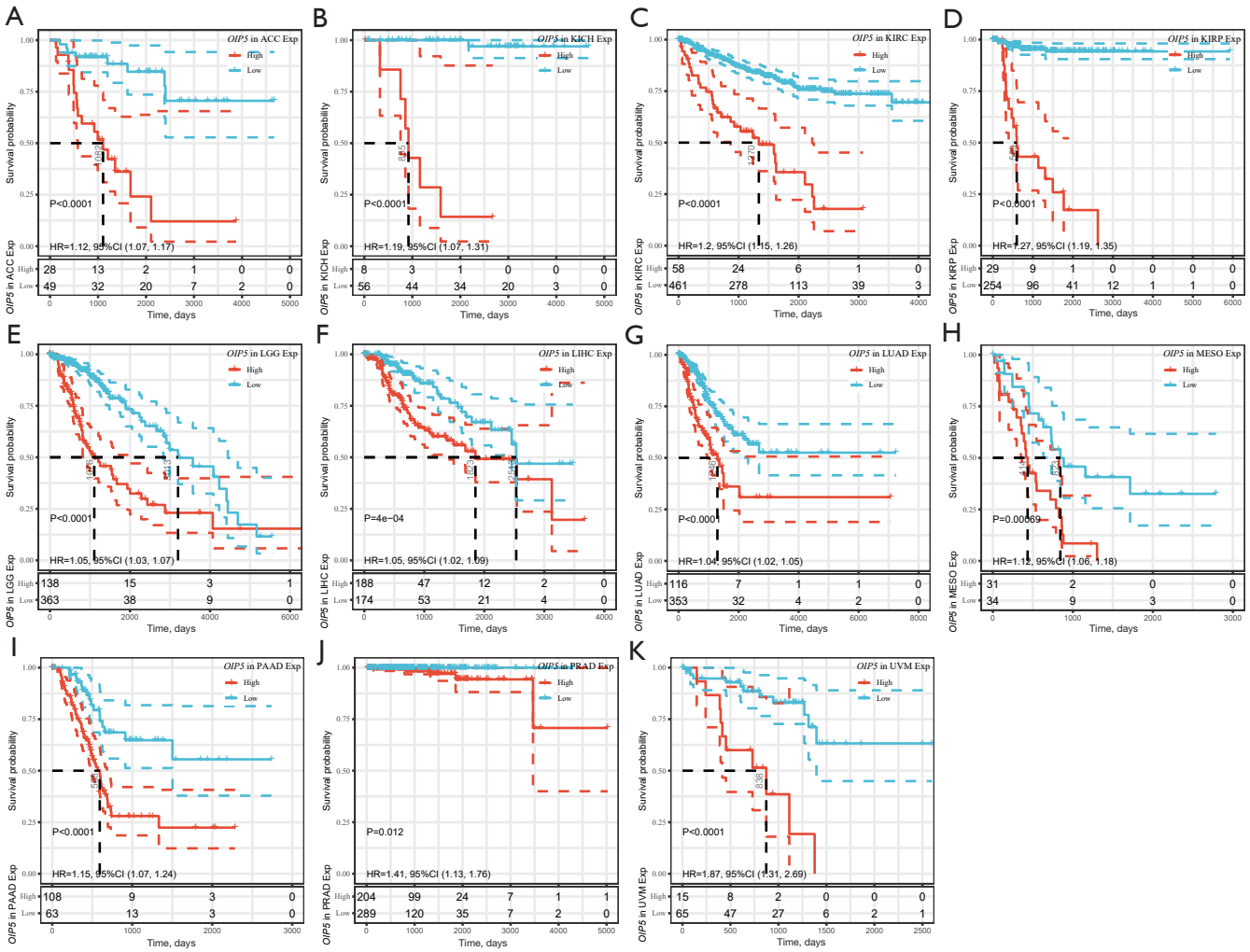

Figure 6 Kaplan-Meier analysis of progression-free survival according to *OIP5* expression in different tumors. (A) ACC, (B) KICH, (C) KIRC, (D) KIRP, (E) LGG, (F) LIHC, (G) LUAD, (H) MESO, (I) PAAD, (J) PRAD, and (K) UVM.

classified into high or low *OIP5* expression groups based on the median *OIP5* expression. Surprisingly, *OIP5* showed enrichment in the cell cycle, base excision repair, homologous recombination, DNA replication, the p53 signaling pathway, and mismatch repair pathways (*Figure 10B*).

Discussion

In recent years, targeted therapy has brought patients with cancer hope for a cure; however, the lack of effective targets has hindered the optimization of this anticancer therapy. Increasing evidence of the crucial effects of cancer-testis specific genes on tumor development has provided some new potential targets for cancer therapy (12,22). *OIP5*, a cancer-testis specific gene, plays an important role in centromere protein A (CENPA) recruitment to the centromere during mitosis (23,24). It also affects chromatin organization and controls the cell cycle. The mitotic rate of a cancer cell represents a vital manifestation of its proliferation ability, proliferation ability often predicts dismal prognostic outcomes. LncRNA *OIP5*-AS1 (Opa-InteractionProtein5 antisense RNA1) can bind to and negatively regulate the activity of multiple cellular RNAs and microRNAs, including cyclin G associated kinase and ELAV like RNA binding protein 1. Overexpression of *OIP5*-AS1 can inhibit the survival, colony formation, invasion and migration of multiple myeloma cells in vitro, induce cell cycle arrest in G1 phase, induce apoptosis,

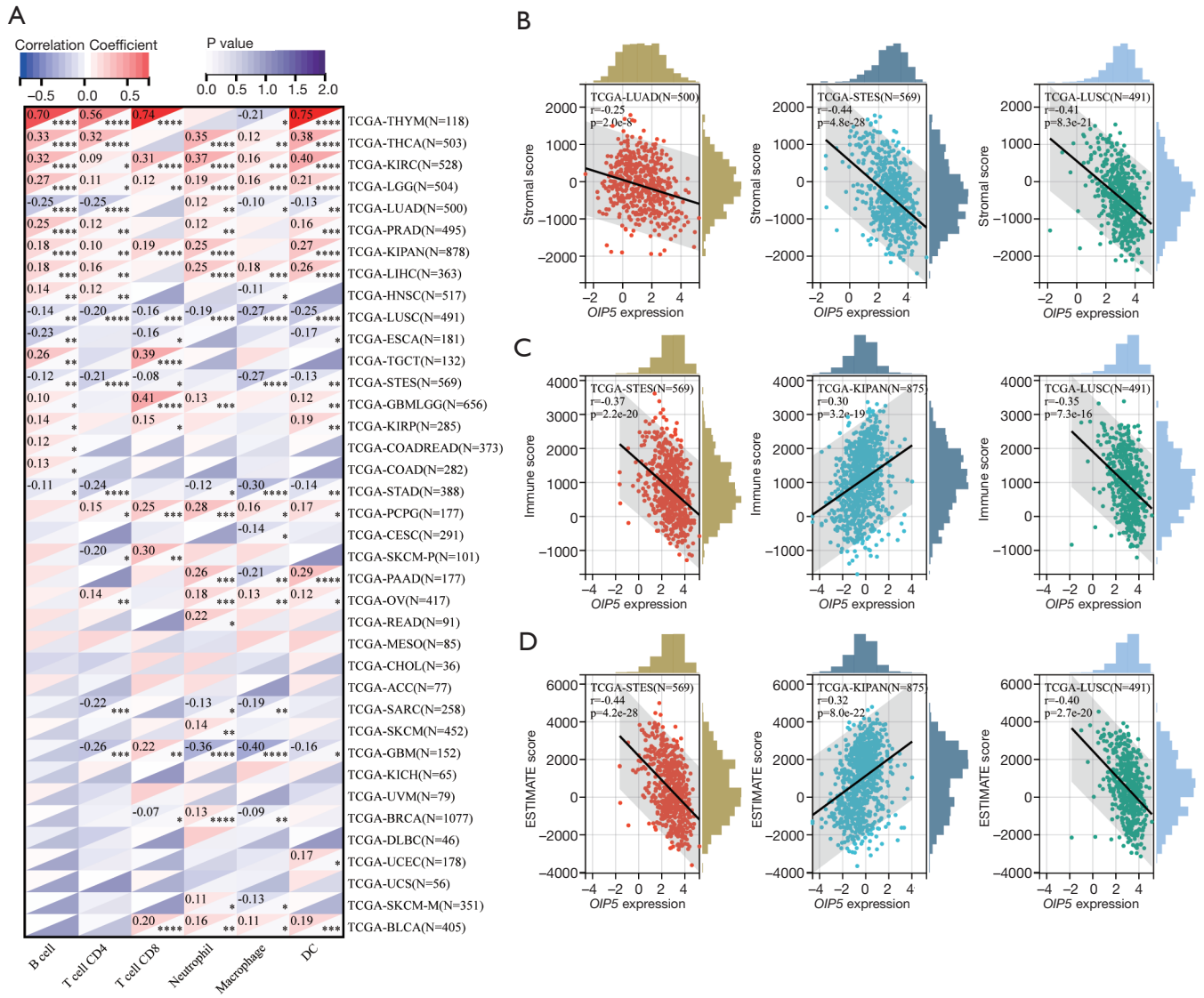

Figure 7 Correlations between *OIP5* expression and tumor-infiltrating immune cells and tumor microenvironment indicators. (A) Results of pan-cancer correlation analysis between *OIP5* expression and B cells, $CD4^+$ T cells, $CD8^+$ T cells, neutrophils, macrophages, and dendritic cells. Representative results of correlation analysis between *OIP5* expression and the (B) stromal, (C) immune, and (D) ESTIMATE scores. *, P<0.05; **, P<0.01; ***, P<0.001; ****, P<0.0001. TCGA, The Cancer Genome Atlas; ESTIMATE, Estimation of STromal and Immune cells in MAlignant Tumors using Expression data.

and inhibit tumor formation *in vivo* (25). Therefore, in this study, a pan-cancer analysis of *OIP5* expression was performed to evaluate its role in prognosis, immunity, and metabolism, as well as its therapeutic potential.

First, we analyzed the differential *OIP5* expression in tumor cells and healthy samples. In normal tissues, *OIP5* was most significantly up-regulated in the bone marrow and testis, whereas it was down-regulated in the heart and pancreas. We found that the expression level of *OIP5* was correlated with the proliferative activity of the tissue. This result is consistent with the reported role of *OIP5* in the mitotic process and its effect on the cell cycle. Based on the analysis of the differential expression of *OIP5* in tumor and paired healthy samples, *OIP5* expression was found to be increased in all tumors except kidney chromophobe and pheochromocytoma and paraganglioma. These findings

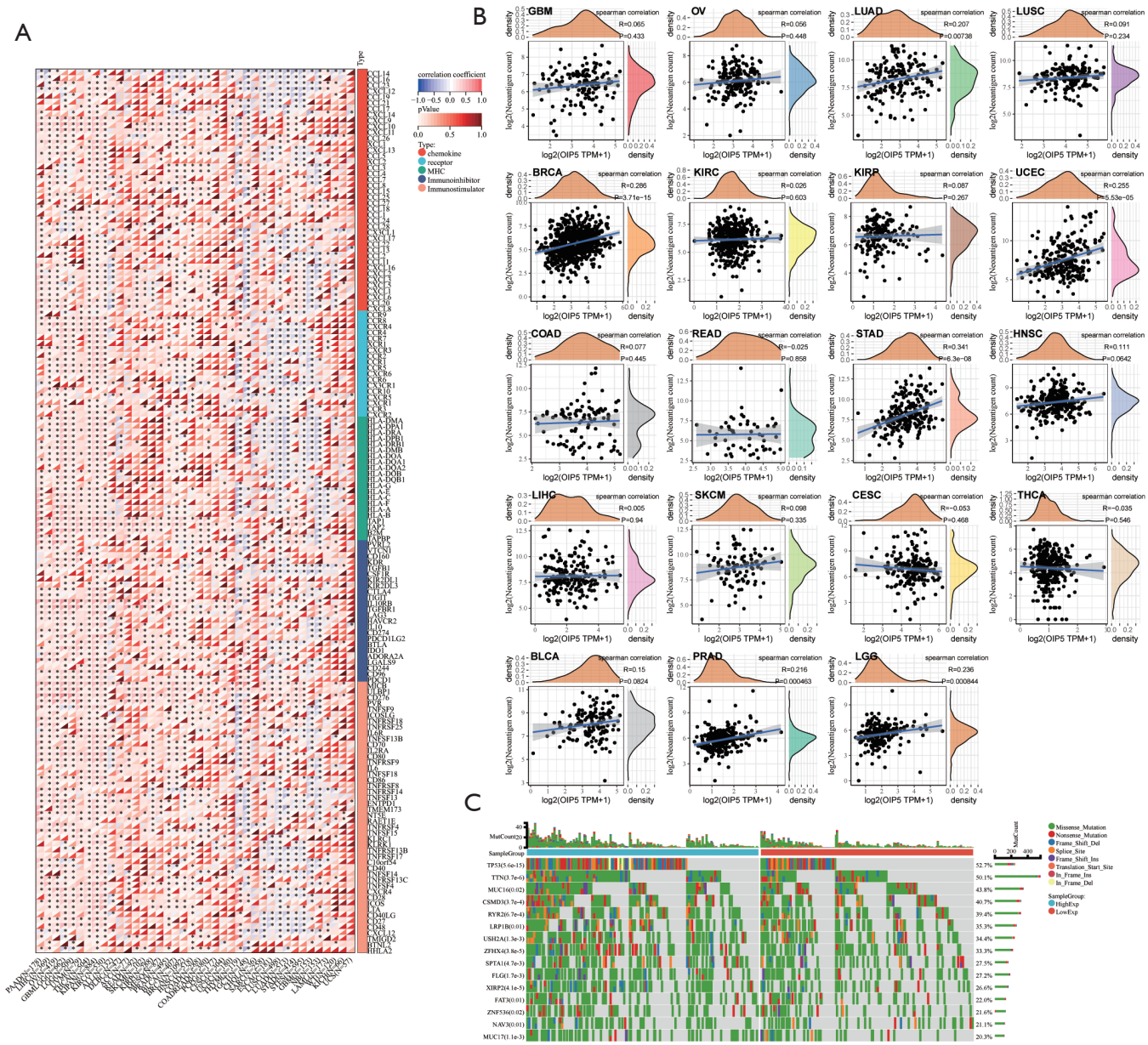

Figure 8 Correlations of *OIP5* expression level with immune regulation, neoantigens, and gene mutation. (A) Pan-cancer correlations between *OIP5* expression and 150 common immunomodulatory molecules. (B) Pan-cancer correlations between *OIP5* expression and various neoantigens. (C) Waterfall plot representing gene mutations in 514 patients with LUAD from The Cancer Genome Atlas. TPM, transcripts per million.

corroborate those of previous studies and the reported characteristics of *OIP5* as a cancer-testis specific gene (8,26,27). Examination of the effect of *OIP5* expression level on OS, DSS, DFS, and PFS in various cancers showed that *OIP5* up-regulation predicted a dismal prognostic outcome in multiple cancers. These results highlight the potential of *OIP5* to become a new prognostic biomarker of pan-cancer.

Of note, in THYM, increased expression of *OIP5* predicted a better prognosis and was also associated with the promotion of immune cell infiltration. The immune system plays an important role in tumor genesis and progression, and tumor occurrence is often associated with

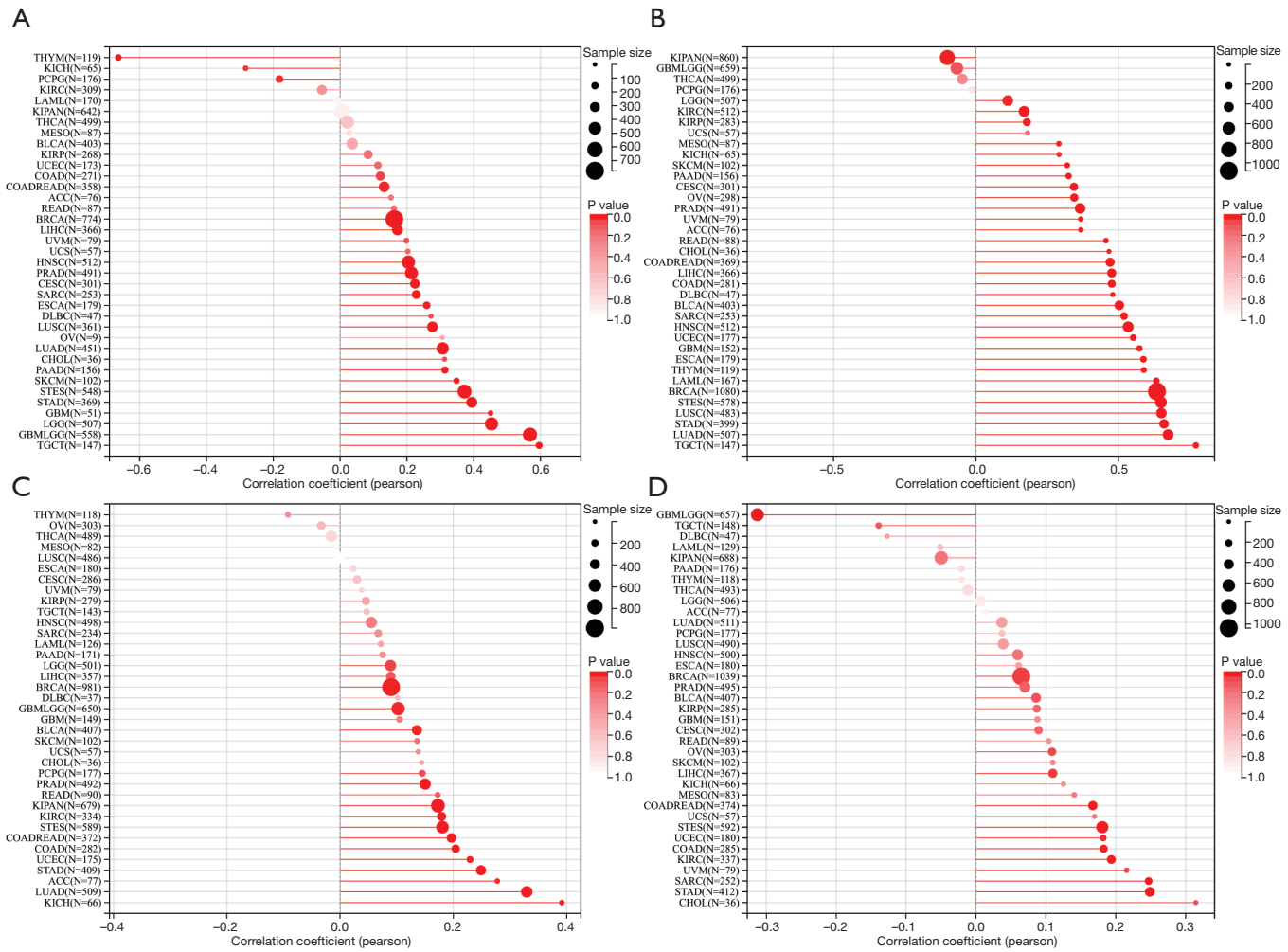

Figure 9 Correlations of *OIP5* expression levels with DNA methylation-based stemness score, mRNA expression-based stemness score, tumor mutational burden, and microsatellite instability. Bubble chart of the correlations between *OIP5* expression and (A) DNA methylation-based stemness score, (B) mRNA expression-based stemness score, (C) tumor mutational burden, and (D) microsatellite instability.

immune system dysfunction (28). *OIP5* might inhibit TIIC infiltration in the tumor microenvironment. *OIP5*-AS1 level was highly expressed in Cancer-associated fibroblasts, which are the most important stromal cells in the tumor microenvironment, and exosomes derived from cancer-associated fibroblasts promote lung cancer progression through the *OIP5*-AS1/miR-142-5p/PD-L1 axis (29). Linc-*OIP5* in breast cancer cells regulates angiogenesis of human umbilical vein endothelial cells through YAP1/Notch/NRP1 signal circuit in tumor microenvironment (30). Various immune cells, including dendritic cells, macrophages, neutrophils, B cells, and T cells, can infiltrate the tumor microenvironment, which affects tumor development. Our results showed an inconsistent association of *OIP5* expression levels with TIIC levels in different tumors, which may be attributable to the complexity of the TIIC infiltration process. Surprisingly, TIIC levels were positively related to *OIP5* expression in THYM, and prognosis showed a similar trend, whereas the opposite trend was observed in LUAD and glioblastoma. Further research on the association of *OIP5* with tumor immune and stromal scores showed that *OIP5* impacted immune cell infiltration and had significant effects on stromal cell infiltration, which can affect the purity and prognosis of

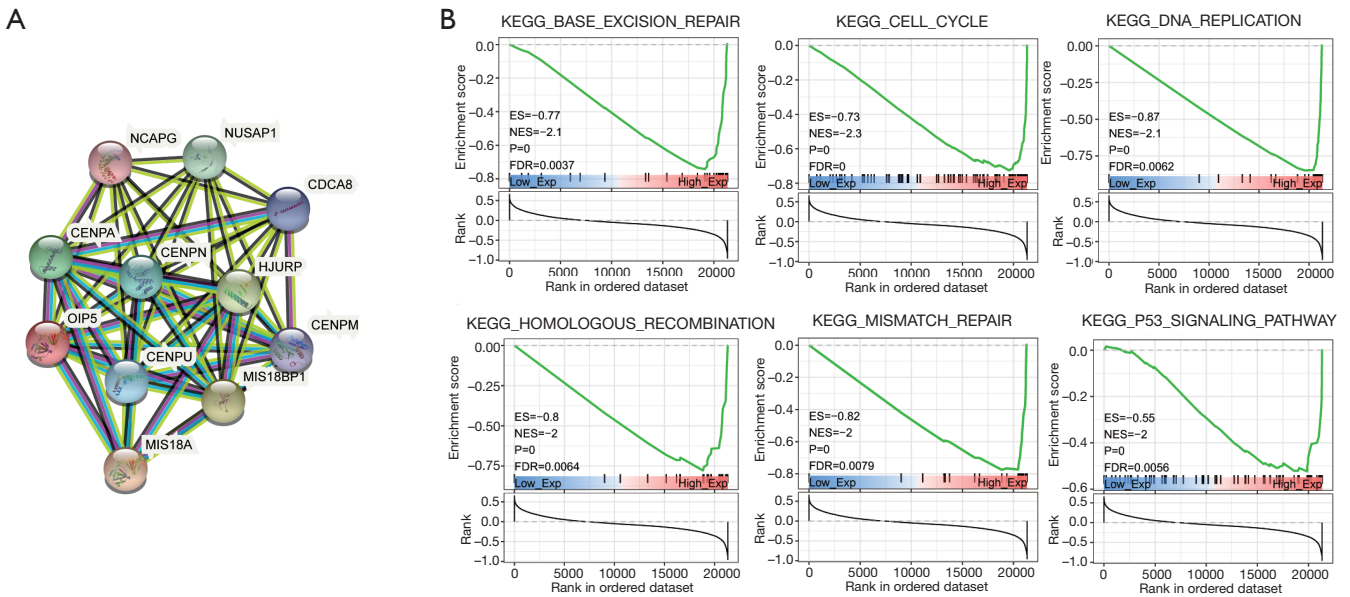

Figure 10 Gene set enrichment analysis of *OIP5* in pan-cancer. (A) Protein-protein interaction analysis of *OIP5*. (B) Kyoto Encyclopedia of Genes and Genomes analysis of *OIP5*.

tumors (15,31). Although the influence of *OIP5* on immune cell infiltration was inconsistent in different tumors, most of the correlations were statistically significant. This result highlights that *OIP5* predicted a dismal prognostic outcome, and the mechanism of it worth investigating.

Extensive research on immune checkpoints, and the advent of immune checkpoint inhibitors (ICIs), has drawn increasing interest in the roles of immune regulation and neoantigen formation in tumor genesis and progression (32). Despite the fact that few diseases can be treated with ICIs at present, the effects of *OIP5* on tumor immune modulation and neoantigen development must be analyzed (33). In this study, association analysis of *OIP5* expression with 150 immune regulatory molecules in different cancers revealed a similar trend to that observed for immune cell infiltration, which was negatively correlated with *OIP5* expression in LUAD, LUSC, and STAD but positively correlated in thyroid carcinoma, the pan-kidney cohort, and ovarian cancer. These results show a consistent and stable effect of *OIP5* on immune regulation in different tumors. Further examination of the relationships of *OIP5* expression level with neoantigen formation and gene mutation frequency in tumors showed positive correlations, further proving that *OIP5* could potentially serve as an antitumor therapeutic target.

The level of tumor differentiation is closely related to cancer stem cell viability, which is reflected by the RNAss and DNAss, with a higher stemness score indicating a lower degree of tumor differentiation (20). Research has proven that TMB and MSI are important indicators for the efficacy of ICI treatment in patients with cancer (34,35). In this study, we examined the relationships of *OIP5* expression with these four indexes to explore how *OIP5* might affect tumor differentiation and immunotherapy sensitivity. In many cancers, the *OIP5* expression level was related to low differentiation and high TMB and MSI. Interestingly, *OIP5* expression in THYM showed a positive correlation with tumor differentiation, which explains its positive prognostic effect. A low differentiation level of tumor cells is always associated with a poor prognosis; however, higher TMB and MSI mean that increased neoantigen production by the tumor can be easily recognized by immune cells, thus improving the therapeutic efficacy of ICIs (36,37). Previous studies have shown that the benefits of ICI therapy are significantly increased for cases with a high TMB compared to those with a low TMB (38-40). Currently, *OIP5* is known to be related to poor survival in diverse cancers; however, with the increasing application of ICIs in tumor treatment, it might also become a positive indicator to predict the therapeutic effect and be related to a positive prognostic outcome. This study serves additional evidence that *OIP5* could serve as a marker for cancer diagnosis and treatment.

To understand the pathophysiological mechanism underlying the role of *OIP5* in pan-cancer, a GSEA was carried out to obtain the functional network and related signal pathways of *OIP5*. Through functional network and signal pathway analysis, *OIP5* was found to be an important player in cell mitosis and to be enriched in the cell cycle, base excision repair, homologous recombination, DNA replication, the p53 signaling pathway, and mismatch repair pathways. These results suggest that *OIP5*, as a key CENP-A recruitment molecule, may ultimately affect tumor genesis and progression by influencing the precise distribution of DNA during the mitotic process (41,42).

Conclusions

In summary, our research demonstrates that *OIP5*, as a cancer-testis specific gene, exhibits high expression and predicts a dismal prognostic outcome in many common cancers. Its expression might influence patient prognosis by affecting the tumor microenvironment and genomic stability. Therefore, *OIP5* has the potential to serve as a therapeutic target and prognostic evaluation index for multiple cancers. The main limitation of our study was its lack of *in vivo* and *in vitro* experiments to prove the findings of our bioinformatic analyses performed on openly accessible databases. Therefore, it is necessary to conduct follow-up validation experiments in the future.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-6640/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-6640/coif). The authors have no conflicts of interest to declare.

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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Supplementary

Table S1 List of tumors

Abbreviation	Tumor name
ACC	Adrenocortical carcinoma
BLCA	Bladder cancer
BRCA	Breast cancer
KICH	Kidney chromophobe
KIRC	Kidney renal clear cell carcinoma
KIRP	Kidney renal papillary cell carcinoma
LGG	Low-grade glioma
LIHC	Liver hepatocellular carcinoma
LUAD	Lung adenocarcinoma
LUSC	Lung squamous cell carcinoma
MESO	Mesothelioma
PAAD	Pancreatic adenocarcinoma
PCPG	Pheochromocytoma and paraganglioma
PRAD	Prostate adenocarcinoma
STAD	Stomach adenocarcinoma
THYM	Thymoma
UVM	Uveal melanoma

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