Bioinformatic analysis of SERINC2 with the prognosis and immune infiltration of stomach adenocarcinomas

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Research Article

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Abstract

Serine Incorporator 2 (SERINC2) is a member of SERINC family, which can incorporate serine into membrane lipids and contributes to the biosynthesis of membrane lipids. SERINC2 has been reported to be associated with tumor progression. However, the expression and function of SERINC2 in stomach adenocarcinomas (STAD) is still unclear. TIMER and GEPIA Database analysis confirmed the high expression of SERINC2 in STAD. Kaplan-Meier Plotter Database analysis showed that STAD patients with high expression level of SERINC2 had low post-progression survival, progression free survival and overall survival. However, gene alterations of SERINC2 have no significant influence on the prognosis of STAD. Moreover, we found that SERINC2 expression was negatively correlated with infiltrating levels of $CD4^+$ and $CD8^+$ T cells, macrophages, neutrophils and dendritic cells in STAD via TIMER. Further analysis from the LinkedOmics database suggested that the co-expressed genes of SERINC2 were enriched in the metabolic process and immune response. Three hub genes, S100A14, RAB25 and FXYD3, were identified through protein-protein network. Among the hub genes, RAB25 was also highly expressed and negatively associated with the survival of STAD patients. These results suggest that SERINC2 is highly expressed in STAD, leading to a poor prognosis and low infiltrating levels of immune cells. The function of SERINC in STAD may be associated with metabolic regulation and RAB25. Therefore, we suggest that it can be an effective biomarker for the diagnosis of STAD.

1. Introduction

Globally, Gastric cancer is the fifth most common malignant disease and the fourth leading cause of cancer deaths, which is a noticeable public health issue for its bad incidence and prognosis[1]. Gastric cancer has different phenotypes for its cellular and molecular heterogeneity. Stomach adenocarcinomas (STAD) is the most common pathological subtype[2]. Despite advances in early diagnosis, surgical, radiotherapy and adjuvant chemotherapy, STAD is still one of the most aggressive malignancies with high morbidity and mortality[3]. Although new target therapies based on molecular mechanisms associated with gastric cancer have been developed, the clinical efficacy is far from satisfactory. Therefore, a better understanding of the key molecules of STAD prognosis through integrated bioinformatics has important clinical value for the effective treatment of STAD.

Serine incorporator 2 (SERINC2), a transmembrane protein, is one of the SERINC (also known as TDE) family. SERINC family consists of five paralogous members, termed SERINC1-5. They have the ability to incorporate a polar amino acid serine into membranes and facilitate the biosynthesis of multiple membrane lipids, such as phosphatidylserine andsphingolipid molecules[4]. Previous study of SERINC family has focused on its role in viral infectivity, which is best known as a restriction factor for viral infectivity[5–7]. Recently, SERINC proteins have also been reported to be associated with cancer progression. Both human and mice SERINC proteins are always upregulated in tumor tissues[8–10]. In 2018, Zeng *et al* used shRNA to suppress SERINC2 expression in lung cancer cells. They found that knockdown of SERINC2 obviously inhibited cell proliferation, migration and invasion[11]. And

bioinformatics analysis by Qi *et al* showed that SERINC2 is a prognostic predict of low grade glioma[12]. However, whether SERINC2 is an effective biomarker of STAD remains unclear. Also, the biological functions of SERINC2 in STAD need to be elucidated.

In this study, to better explore the role of SERINC2 in STAD, we explored the association of SERINC2 expression with STAD patients' survival and its potential regulation mechanism by analyzing the data from TCGA and GEO datasets. Our results will provide an insight into the function of SERINC2 in STAD and a theoretical basis for the early diagnosis, prognosis, and targeted therapy of STAD.

2. Materials And Methods

2.1 TIMER Database analysis

TIMER (https://cistrome.shinyapps.io/timer/) is a database to analyzes the immune infiltration abundances of 10897 samples across 32 cancer types providing from The Cancer Genome Atlas (TCGA) [13]. TIMER employed deconvolution to speculate the number of tumor-infiltrating immune cells through using gene expression profiles[14]. We used TIMER to assess the difference in expression of SERINC2 in different types of cancer and analyze the correlation of SERINC2 expression with the abundance of immune infiltrates. We also analyzed the relation between SERINC2 copy number variation (CNV) and immune cell infiltration in the TIMER database.

2.2 GEPIA Database analysis

Gene Expression Profiling Interactive Analysis (GEPIA) (http://gepia.cancer-pku.cn/index.html) is a database web for analyzing RNA-seq data from 9736 tumor samples and 8587 normal control samples in the TCGA and GTEx data sets[15]. We used GEPIA to explore the expression of SERINC2 in STAD.

2.3 Kaplan-Meier Plotter Database analysis

The Kaplan Meier plotter is an online database that could assess the impact of genes on patient survival across 21 cancer types (http://kmplot.com/analysis/)[16]. Patients were divided into high and low expression group to explore the effect of SERINC2 expression on the survival of STAD patients. The log-rank *P* value and the hazard ratio (HR) with 95% confidence interval were also computed.

2.4 LinkedOmics Database analysis

LinkedOmics is a online tool that contains 32 TCGA Cancer types data and 10 Clinical Proteomics Tumor Analysis Consortium (CPTAC) cancer cohorts data (http://www.linkedomics.org/login.php)[17]. We used the LinkFinder module of LinkedOmics to filtrate the differentially expressed genes associated with SERINC2 through selecting RNA-seq data in TCGA STAD cohort (n = 415). The correlation of results was tested by the Pearson's correlation coefficient. The volcano plots and heat maps were used to present analysis results. In LinkInterpreter module of LinkedOmics, Gene Set Enrichment Analysis (GSEA) was performed the results of enrichment analysis including Gene Ontology (GO) analysis (cellular component

(CC), biological process (BP), molecular function (MF)) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis.

2.5 cBio Cancer Genomics Portal Database analysis

cBioPortal (http://cbioportal.org) is a open-access web resource which be applied to explore visual and multidimensional cancer genomics datasets with resources from 20 cancer studies including more than 5,000 tumor samples[18]. We used cBioPortal to analyze SERINC2 mutation in the TCGA STAD sample.

2.6 STRING Database Analysis AND Cytoscape software analysis

STRING (https://string-db.org/) is a constantly updated database and could seek for interactions between known proteins and predicted protein interactions. We established a protein-protein interactive (PPI) network by using the top 100 significantly positive co-expressed genes. Cytoscape (https://cytoscape.org/) is a graphical display network software for analysis and editing the PPI network. After that, the hub proteins were determined by the MCODE plugin.

2.7 Statistical analysis

Survival curves were generated by KaplanMeier plots. The results of KaplanMeier plots and GEPIA are displayed with HR and P or Cox P-values from a log-rank test. Correlation between two groups was determined using Pearson correlation coefficient analysis. P-values < 0.05 were considered statistically significant.

3 Results

3.1 The increased expression of SERINC2 in STAD

We initially analyzed the differential expression of SERINC2 in multiple malignancies and normal tissues via the RNA-seq data from TCGA. As shown in Fig. 1A, compared with adjacent the normal tissues, the expression level of SERINC2 was higher in BLCA (bladder urothelial carcinoma), BRCA (breast invasive carcinoma), CHOL (cholangiocarcinoma), ESCA (esophageal carcinoma), HNSC (head and neck squamous cell carcinoma), LIHC (liver hepatocellular carcinoma), LUAD (lung adenocarcinoma), LUSC (lung squamous cell carcinoma), STAD (stomach adenocarcinoma), THCA (thyroid carcinoma) and UCEC (uterine corpus endometrial carcinoma). Conversely, in COAD (colon adenocarcinoma), KICH (kidney chromophobe), KIRC (kidney renal clear cell carcinoma) and READ (rectum adenocarcinoma), the expression level of SERINC2 was significantly lower than that in normal tissues. We then used the GEPIA database to confirm the high expression levels of SERINC2 in STAD. Results revealed that the mRNA level of SERINC2 was remarkably higher in STAD than that in normal tissues (Fig. 1B and C).

3.2 Association of SERINC2 expression and mutation with the prognosis of STAD patients

We further explored whether the survival of STAD patients was affected by SERINC2. Kaplan-Meier Plotter tools were used to analyze the correlation between SERINC2 mRNA levels and the survival of patients with STAD. As shown in Fig. 2A-C, the patients with higher SERINC2 expression level had worse overall survival (OS), post-progression survival (PPS) and progression free survival (PFS) than those with lower SERINC2 level ($P < 0.05$). Generally, STAD was negative correlated with mRNA expression of SERINC2 in terms of PPS, PFS and OS. In order to better understand the relevance and potential mechanism of SERINC2 in STAD, we explored the relationship between the SERINC2 expression and clinical characteristics of STAD patients in the Kaplan-Meier plotter database. As shown in table1, the high SERINC2 expression level was significantly associated with worse OS, PPS and PFS in patient gender, stage, T stage, N stage, M stage and Lauren classification, with the exception of T stage 4, two types of Lauren classification ($P < 0.05$). There are significantly association between high SERINC2 expression and worse OS and PPS in stage N1 and N2. In addition, high SERINC2 expression was significantly related with worse PPS in stage N3. High SERINC2 expression was also significantly related with worse OS, PPS and PFS in stage N1 + N2 + N3. Generally, the above results indicated that SERINC2 expression level affected the prognosis of STAD patients with lymph node metastasis.

Occurrence and prognosis of most tumors are related to gene alterations. Here, we evaluated the association of SERINC2 mutation with the prognosis of STAD patients. Gene alterations in SERINC2 were found to occur in a total of 14 out of 478 sequenced cases in the data obtained from the OncoPrint schematic of cBioPortal (Fig. 2D). The information of the mutation sites, mutation types and case number is shown in the mutation diagram (Fig. 2E). In this diagram, different colors represent the corresponding mutation types. Overall, we found seven mutations of SERINC2, including four missense mutations, one splice mutation, one inframe mutations and one truncating mutation, in sequenced STAD patients. The mutation sites all occurred in Serinc. However, the KM curves analysis of the prognostic value between the SERINC2 altered group and the unaltered group showed no significance (Fig. 2F). These results suggested that the effect of SERINC2 on the prognosis of STAD was not due to its mutation.

3.3 SERINC2 expression is correlated with immune infiltration level in STAD patients

Given the key role of immune infiltration in the tumor development in diverse types of cancer, we further evaluated the relationship between SERINC2 expression and immune cell infiltration levels by using TIMER. Our results showed that the expression of SERINC2 was negatively correlated with the infiltration levels of $CD8^+$ T cells ($r = -0.25$, $P = 1.15E-6$), CD4 + T cells ($r = -0.212$, $P = 4.25E-5$), macrophages ($r = -0.288$, $P = 1.62E-8$), neutrophils ($r = -0.273$, $P = 8.91E-8$) and dendritic cells ($r = -0.314$, $P = 5.82E-10$) in STAD (Fig. 3A). Meanwhile, we analyzed the correlation between SERINC2 copy number variation (CNV) and immune infiltration level using the somatic copy number alteration (SCNA) module in the TIMER database. The results revealed a closely association between SERINC2 CNV with the degree of infiltration of B cell, $CD4^+$ T cell, macrophages, neutrophils and dendritic cell (Fig. 3B). Moreover, the correlation between SERINC2 expression and gene markers of different immune cell was analyzed through TIMER.

As listed in table S1, multiple immune cell markers were significantly correlated with SERINC2 expression. The $CD8^+$ T cell marker, the general T cell marker, the monocyte marker, the M2 Macrophage marker and the T cell exhaustion marker had strong correlations with SERINC2 expression. These findings strongly suggest that SERINC2 plays a specific role in immune infiltration in STAD.

3.4 Co-expression genes correlated with SERINC2 in STAD

To further explore the potential biological function of SERINC2 in STAD, we analyzed the co-expressed genes associated with SERINC2 in 415 STAD cases by mining the LinkedOmics database. Results showed that 4811 genes on the right of 0, represented by red dots in Fig. 4A, were positively associated with SERINC2. Moreover, there were 6382 genes, represented by dark green dots, having a negative correlation with SERINC2 ($p < 0.05$). The top 50 significant genes positively and negatively correlated with SERINC2 were shown by the heat map, respectively (Fig. 4B and C). The details of co-expressed genes is summarized in Table S2. Among the positive co-expression genes, DDR1, ELMO3, PTK6 were chose to confirm the correlation with SERINC2 through GEPIA database. SERINC2 expression was strongly correlated with DDR1 ($r = 0.5362$, $p = 2.933e-32$), ELMO3 ($r = 0.529$, $p = 2.648e-31$) and PTK6 ($r = 0.5272$, $p = 4.575e-31$) (Fig. 4D-F).

We further performed the GO and KEGG functional enrichment analysis of these co-expressed genes by GSEA in LinkedOmics. Biological process (BP) enrichment analysis showed that the co-expressed genes of SERINC2 mainly participated in epidermis development, cellular aldehyde metabolic process and isoprenoid metabolic process (Fig. 4G). Cellular component (CC) enrichment analysis showed that the co-expressed genes of SERINC2 mainly participated in cornified envelope, mitochondrial protein complex and respiratory chain (Fig. 4H). Molecular function (MF) enrichment analysis showed that the co-expressed genes mainly participated in oxidoreductase activity acting on CH-OH group of donors and a heme group of donors and electron transfer activity (Fig. 4I). KEGG pathway analysis indicated these genes were significantly correlated with immune signaling pathway and responses, including primary immunodeficiency, antigen processing and presentation, T cell receptor signaling pathway and natural killer cell mediated cytotoxicity (Fig. 4J). These results suggest that SERINC2 expression has a broad effect on the global transcriptome of STAD and immune signaling pathway.

3.5 The PPI network of co-expression gene was established

A protein-protein network was built by using the top 100 significantly positive co-expressed genes of SERINC2 in STRING database. As shown in Fig. 5A, PPI network was composed of 56 nodes and 76 edges. After using MCODE plug-in, S100A14, RAB25 and FXYD3, highlighted in yellow, was identified as the hub genes. We further performed survival analysis of the 3 hub genes using the Kaplan-Meier Plotter database. The expression level of RAB25 was significantly related to the OS of STAD. STAD patients with high expression of RAB25 had poor prognosis (Fig. 5B). Moreover, RAB25 was significantly up-regulated in STAD tissue (Fig. 5D). Based on the results, we speculated that the association between SERINC2 and RAB25 is a contributing factor for its prognostic value in STAD.

4 Discussion

SERINC2 is a transmembrane protein that incorporate serine into membrane lipids during synthesis of sphingolipid and phosphatidylserine. It is first identified as an effector molecule that facilitates the biosynthesis of lipids in nervous system[4]. Researches on SERINC2 mainly focus on its role in mental disorder, including bipolar disorder, alcohol dependence and autism spectrum disorder. However, our understanding of the role of SERINC2 in canceris is limited and requires further investigation. Recently, a bioinformatics analysis showed that SERINC2 is a potential prognostic marker in glioma patients[12]. In addition, in vitro assay shows that SERINC2-knockdown suppresses cell proliferation, migration and invasion for lung adenocarcinoma[11].

In this study, we explored the prognostic role of SERINC2 in STAD and its relationship with immune cell infiltration for the first time. Consistent with previous findings in other tumors, we found that the mRNA level of SERINC2 were higher in STAD than in normal tissues by analyzing the RNA-seq data from TCGA. Then we examined the association of SERINC2 expression with the survival of STAD patients. Higher SERINC2 expression predicted shorter OS, FPS and PPS in STAD patients. High expression of SERINC2 was associated with poor prognosis of patients have STAD indicating that SERINC2 may be a potential predictor of STAD cancer prognosis. Occurrence and prognosis of most tumors are related to gene alterations. Only 3% mutated cases were found in the cBioportal database, indicated that the mutation frequency of SERINC2 was very low. Comparing altered group with the unaltered group, there was no significant difference in the probability of OS between them.

As a systemic disease, cancer can influence its micro-environment by inducing functional and compositional changes to the immune system[19]. Tumor-promoting inflammation and avoiding immune destruction are known as the hallmarks of cancer[20]. Therefore, we further explored the relationship between SERINC2 expression and immune infiltration in STAD via TIMER database. Our analysis shows that level of SERINC2 was negatively correlated with the infiltration levels of $CD8^+$ T cells, $CD4^+$ T cells, macrophages, neutrophils and dendritic cells. In addition, The level of SERINC2 expression can impact diverse immune marker sets in STAD patients. These results suggest that SERINC2 may be involved in the immune response to the tumor microenvironment of STAD. Especially, $CD8^+$ T cells, dendritic cells (DCs), macrophages, and neutrophils comprise the anti-tumor immune system.

Finally, the co-expression genes related to SERINC2 in STAD was analyzed through the Linkedomics database. GSEA function analysis indicated that co-expression genes participated in metabolic process and immune signaling pathway via GO and KEGG pathway analysis. metabolism reprogramming is known as a fundamental hallmark of malignant, which may be a key factor for the role of SERINC2 in the STAD development. The co-expression genes of SERINC2 were enriched in immune signaling pathway and response, which is consistent with the analysis from TIMER database. These results strongly suggest that SERINC2 plays a specific role in immune infiltration in STAD. We then analyze the interactions between co-expression genes and SERINC2 through STRING Database. As a result, 3 hub genes,S100A14, RAB25 and FXYD3, was identified. RAB25 has been reported to play a oncogene role in gastric cancer. We

also revealed its abnormal expression and correlation with the prognosis in STAD. The biology function of SERINC2 may be related to RAB25.

5 Conclusion

This study systematically analyzed public sequencing data to guide the research of SERINC2 in STAD. Our work shows that SERINC2 is highly expressed in STAD and associated with the poor prognosis and low immune infiltration. Further analysis shows that the role of SERINC2 in STAD may be associated with metabolic process and tumor related immune regulation. In general, SERINC2 may be identified as an important potential biomarker for STAD diagnosis.

Declarations

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Conflicts of interests: none

Author contributions: Yu Haixia and Fang Xianjun conceived the project. Yu Haixia, Ling Qiaoyun and Zhai Chi participated in data analysis. The first draft of the manuscript was written by Haixia Yu and revised by Xianjun Fang. All authors commented on previous versions of the manuscript and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

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Figures

Figure 1

SERINC2 expression is higher in STAD than in normal tissues. (A) SERINC2 expression levels in different type of human cancers from TCGA database were determined by TIMER. (B and C) Increased SERINC2 expression in STAD compared with normal tissues in the TCGA and GTEx data setsd was determined by GEPIA. *P < 0.05, **P < 0.01, ***P < 0.001.

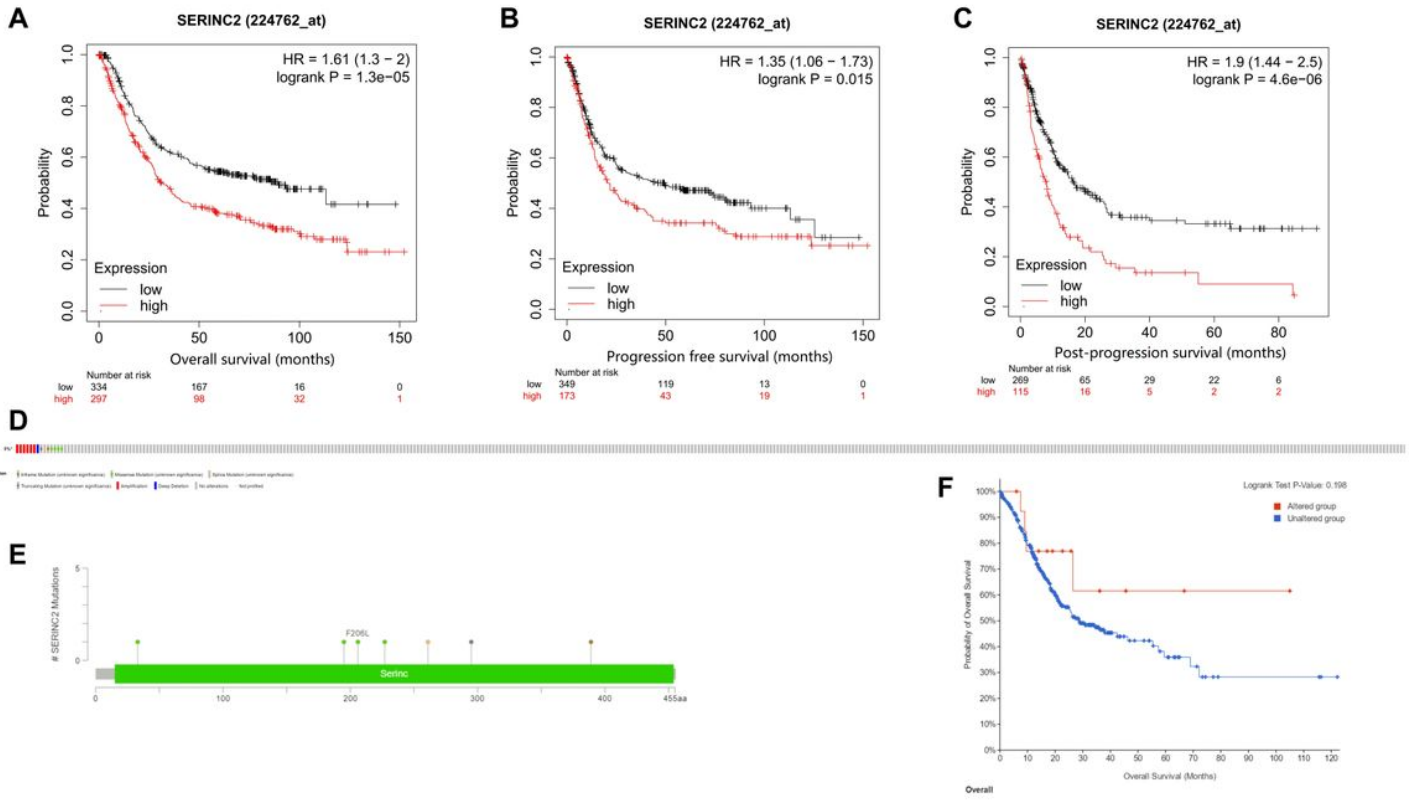

Figure 2

The prognostic value of mRNA level and gene alteration of SERINC2 in STAD patients. (A-C) Logrank test was used in analysis of OS/PFS/PPS. (D) The genetic alterations in SERINC2 in STAD tissues. (E) An overview of genetic alternations of SREINC2 in STAD. (F) Kaplan-Meier survival curves were used to analyze the correlation of SERINC2 alterations with the OS of STAD patients.

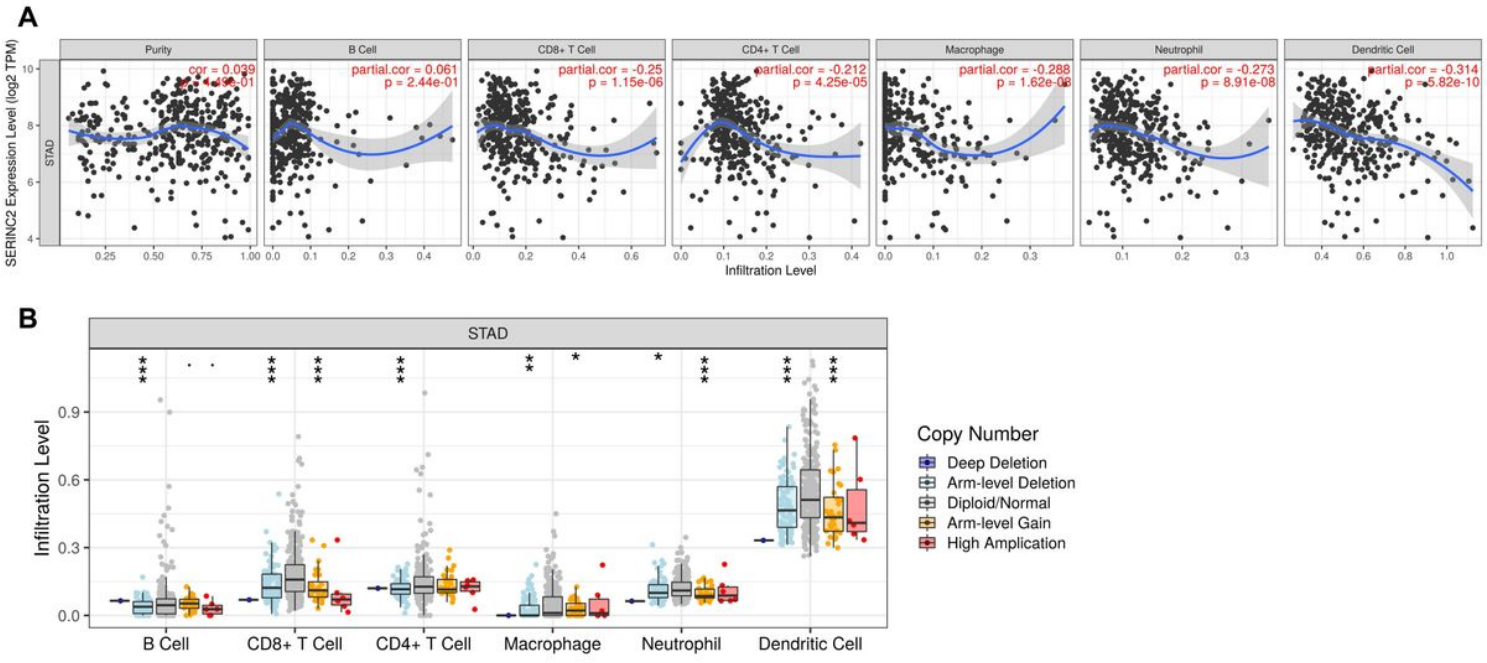

Figure 3

The correlation between SERINC2 expression and immune infiltration level in STAD. (A) SERINC2 expression is negatively related to infiltration levels of CD8+ T cells, CD4+ T cells, macrophages, neutrophils, and dendritic cells in STAD. (B) SERINC2 CNV affects the infiltrating levels of B cell, CD8+ T cell, CD4+ T cell, macrophages, neutrophils and dendritic cell in STAD. *P < 0.05, **P < 0.01, ***P < 0.001.

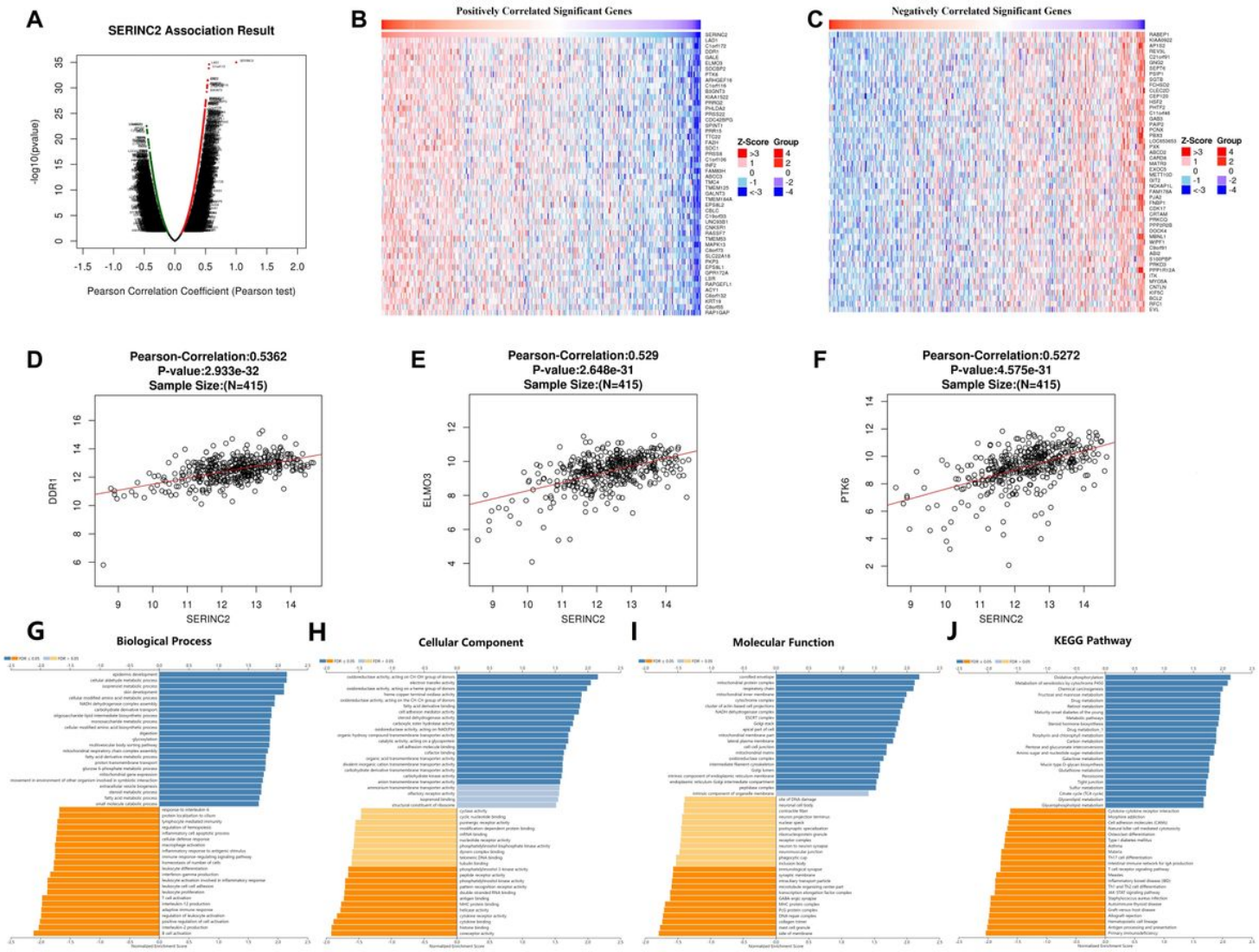

Figure 4

Co-expressed genes of SERINC2 in STAD. (A) Pearson test to analyze the correlations of SERINC2 with differentially expressed genes in STAD, red points indicate positively correlated genes and green points indicate negatively correlated genes. (B and C) Heat maps show the top 50 significant genes positively and negatively with SERINC2 in STAD. (D-F) GEPIA was used to confirm the correlation between the top significant genes (DDR1, ELMO3 and PTK6) and SERINC2 in STAD. The Biological process (G), Cellular component (H), Molecular function (I) and KEGG pathway (J) of SERINC2 co-expression genes in STAD were analyzed using GSEA.

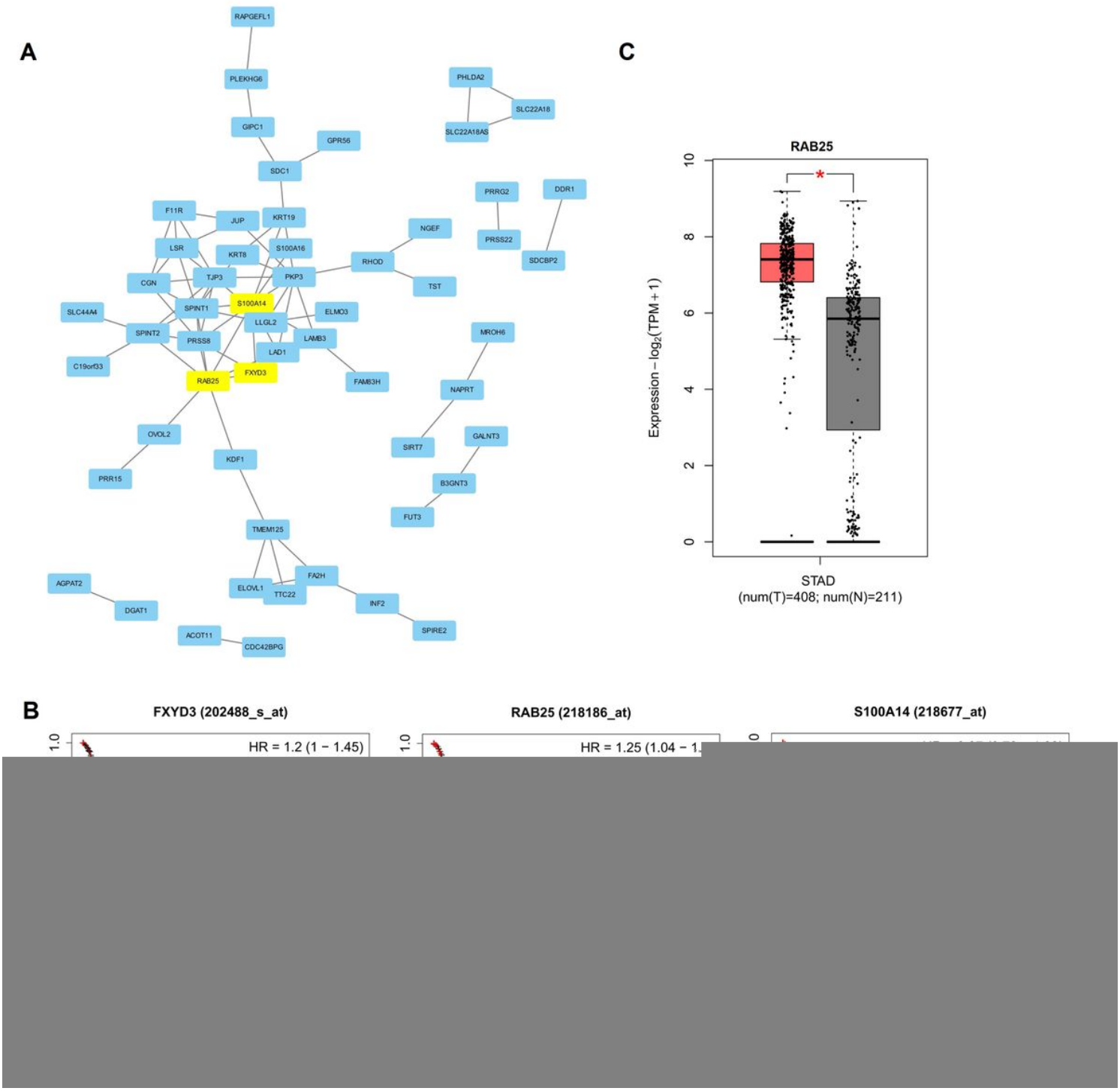

Figure 5

Protein–protein interaction (PPI) network of SERINC2 co-expression gene (top 100). (A) The Protein–protein interaction network of co-expression gene. The MCODE analysis was used to identify the hub genes S100A14, RAB25 and FXYD3. (B) The correlation between the hub genes expression level and OS of STAD was analyzed in the Kaplan-Meier plotter database. (C) Increased RAB25 expression in STAD compared with normal tissues in the TCGA database. *P < 0.05.

Supplementary Files

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- Table1.xlsx
- TableS1.xlsx
- TableS2.xlsx