ORIGINAL RESEARCH

A Pan-Cancer Analysis of the Role of Selenoprotein P mRNA in Tumorigenesis

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Background: Selenium (Se) exhibits its anti-carcinogenic properties by regulating the redox system. However, the relationship between selenoprotein P (SeP), mRNA (*SELENOP* mRNA) and tumorigenesis remains unclear. Plasma SeP transports Se to various target tissues and has antioxidant characteristics. The present study aimed to explore the multi-faceted pan-cancer properties of *SELENOP* in terms of its tissue-specific expression, prognostic value, immune function, and signaling pathway enrichment.

Patients and Methods: The expression profile of *SELENOP* was determined in 33 tumor types and survival, pathway enrichment, and correlation analyses were conducted based on TCGA database. The relationship between *SELENOP* expression and immune infiltration and macrophage subtype gene markers was investigated using the TIMER and GEPIA.

Results: *SELENOP* gene expression was decreased in many cancer tissues, but was upregulated in brain lower grade glioma (LGG). Furthermore, *SELENOP* expression was associated with a better prognosis in most cancers, but a poorer prognosis in LGG and uterine corpus endometrioid carcinoma (UCEC). Our results showed that *SELENOP* was correlated with infiltration level of six immune cell types, where *SELENOP* also showed a strong correlation with macrophages in some cancer types. However, we failed to determine macrophage polarization in 33 tumor types. *SELENOP* negatively regulated vascular endothelial cell proliferation in LGG and UCEC and epidermal cell differentiation in six tumor types. In contrast, upregulation was related to immune function, including T cell activation, B cell-mediated immunity, adaptive immune response and immune response regulation cell surface receptor signaling pathways in another six tumor types.

Conclusion: These findings highlighted the tissue-specific expression, prognostic value and immune characteristics of *SELENOP* in pan-cancer, and provided insights for illustrating the role of *SELENOP* in tumorigenesis.

Keywords: selenoprotein P, pan-cancer, immune infiltration, prognosis, tissue-specific expression

Introduction

Selenium (Se) is a trace element that plays a crucial role in human health. Its biological function is mainly attributed to its presence in selenoproteins.[1] Se incorporates into the protein via the amino acid selenocysteine (Sec).[2] Se metabolic system plays a key role in this process. Dietary Se is absorbed and the liver synthesizes and exports selenoprotein P (SeP). Then, SeP (encoded by *SELENOP*) circulates in the blood to transport Se to other tissues and organs.[3] The transported Se is converted into intracellular selenophosphate, which is used to transform tRNA[[ser]sec]-bound serine into Sec.[3,4] Sec-tRNA[[ser]sec] is incorporated

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into polypeptide chains, which finally completes the selenoprotein synthesis.[4] Due to their special physiological domains, selenoproteins exhibit antioxidant activity and regulate Se transport, immune response and thyroid hormone metabolism.[5] Oxidative damage has been demonstrated to play a carcinogenic role. Thus, Se demonstrates its anti-carcinogenic properties by regulating the redox system.[6,7]

Several epidemiological studies have also revealed the benefits of Se in cancer.[8–10] However, an excessive supply of Se may have adverse effects on brain diseases, endocrine system, and cancer.[11] It is worth noting that Se may play several roles in the initiation and development of cancer. Our previous study showed a dual relationship between certain types of cancer and glutathione peroxidases (GPXs) and thioredoxin reductases (TXNRDs) in selenoproteins.[12]

Although Se has a broad anti-carcinogenic effect, specific selenoproteins' contributions to the development of cancer remain unclear. With the rapid development of genomic technology, 25 genes encoding selenoproteins have been found in the human genome.[1] Among them, SeP is a unique plasma selenoprotein, which contains more than one Sec, while human *SELENOP* sequence has as many as ten Sec residues.[13] Therefore, SeP is essential for Se transport to the targeted tissues.[14] SeP is mainly synthesized in the liver, but it is also expressed in other organs, particularly the brain, kidney and testis.[15,16] In addition to its transport function, *SELENOP* also has antioxidant properties in the development of diseases, such as colitis-associated and non-small cell lung cancers.[14,17] *SELENOP* downregulation in prostate cancer leads to oxidative stress and carcinogenesis.[18] There are few studies on the immune function of *SELENOP*, and its potential immune mechanism is typically discussed in terms of proinflammatory immune cells and immune regulation of the liver. The loss of *SELENOP* may increase polarization of M2 macrophages and promote the occurrence of inflammatory tumors.[19] *SELENOP* mRNA is upregulated in patients with chronic hepatitis C. It has also been shown to inhibit retinoic-acid-inducible gene I (RIG-I)-mediated type I IFN response, resulting in persistent hepatitis C virus infection.[20]

Based on the above evidence, *SELENOP* may be related to tumorigenesis due to its Se transport function, antioxidant properties and immune function. Hence, the present study conducted the first pan-cancer analysis of *SELENOP* using multiple datasets and bioinformatics tools. The association between *SELENOP* expression levels and various factors, such as prognosis, genetic alteration, immune cells, tumor microenvironment and signaling pathways, was investigated in order to explore the multifaceted properties pan-cancer properties of *SELENOP*.

Materials and Methods
Collection of TCGA Pan-Cancer Data and Patient Selection
The data used in this study were obtained from the TCGA database (https://portal.gdc.cancer.gov/). The TCGA database is a cancer genomics program of the National Cancer Institute (NCI) and the National Human Genome Research Institute, which includes genomic, epigenomic, transcriptional, and proteomic data for 33 tumor types. The data are widely used in cancer research and offer help to the diagnosis, treatment and prevention of cancer.

11,057 samples were downloaded by open-source software. These samples covered 33 different types of cancer, and comprised 10,327 tumor samples and 730 normal samples. Samples had received other adjuvant treatments were excluded. These data were used to analyze the expression pattern of *SELENOP* in 33 tumor types, the effect of *SELENOP* expression on survival, the association between *SELENOP* expression levels and tumor mutation burden (TMB), microsatellite instability (MSI), mismatch repair (MMR) gene expression, tumor microenvironment and signaling pathways in different cancers.

Expression Analysis of *SELENOP* Based on Multiple Databases
Based on mRNA expression data downloaded from the TCGA database, we analyzed the differences in *SELENOP* expression between tumor and normal tissues in 33 different types of cancer. Detailed information about 33 tumor types is presented in Table 1. Due to the absence or limited number of normal tissues in some cancers, we additively analyzed the expression differences in TCGA-based tumor tissues combined with GTEx normal tissues using the GEPIA2 (http://gepia2.cancer-pku.cn/) online tool.[21]

Based on the UALCAN portal (http://ualcan.path.uab.edu/analysis-prot.html), we validated six cancers at the protein level using the CPTAC dataset, including breast cancer, ovarian cancer, colon cancer, clear cell RCC

Table 1 Summary of Detailed Information for 33 Tumor Types in TCGA Database

Primary Disease Type	ID	Total N	Primary Tumor	Normal Tissue
Adrenocortical cancer	ACC	79	79	0
Bladder urothelial carcinoma	BLCA	430	411	19
Breast invasive carcinoma	BRCA	1217	1104	113
Cervical & endocervical cancer	CESC	309	306	3
Cholangiocarcinoma	CHOL	45	36	9
Colon adenocarcinoma	COAD	512	471	41
Diffuse large B-cell lymphoma	DLBC	48	48	0
Esophageal carcinoma	ESCA	173	162	11
Glioblastoma multiforme	GBM	173	168	5
Head & neck squamous cell carcinoma	HNSC	546	502	44
Kidney chromophobe	KICH	89	65	24
Kidney clear cell carcinoma	KIRC	607	535	72
Kidney papillary cell carcinoma	KIRP	321	289	32
Acute myeloid leukemia	LAML	151	151	0
Brain lower grade glioma	LGG	529	529	0
Liver hepatocellular carcinoma	LIHC	424	374	50
Lung adenocarcinoma	LUAD	585	526	59
Lung squamous cell carcinoma	LUSC	550	501	49
Mesothelioma	MESO	86	86	0
Ovarian serous cystadenocarcinoma	OV	379	379	0
Pancreatic adenocarcinoma	PAAD	182	178	4
Pheochromocytoma & paraganglioma	PCPG	186	183	3
Prostate adenocarcinoma	PRAD	551	499	52
Rectum adenocarcinoma	READ	177	167	10
Sarcoma	SARC	265	263	2
Skin cutaneous melanoma	SKCM	472	471	1
Stomach adenocarcinoma	STAD	407	375	32
Testicular germ cell tumor	TGCT	156	156	0
Thyroid carcinoma	THCA	568	510	58
Thymoma	THYM	121	119	2
Uterine corpus endometrioid carcinoma	UCEC	583	548	35
Uterine carcinosarcoma	UCS	56	56	0
Uveal melanoma	UVM	80	80	0

(Renal cell carcinoma), UCEC (uterine corpus endometrioid carcinoma) and LUAD (lung adenocarcinoma).[22]

Survival Analysis of *SELENOP* in Pan-Cancer

Survival data from TCGA dataset were used to analyze the relationship between *SELENOP* expression and prognosis in patients with different types of tumor by univariate methods. In order to comprehensively analyze the effect of *SELENOP* expression on tumor prognosis, three outcome indicators were included in our study, namely overall survival (OS), progression-free survival (PFS) and disease-specific survival (DSS). Meanwhile, the survival difference of

SELENOP low expression and high expression was explored by Kaplan-Meier analysis according to the above three indicators.

Genetic Alteration Analysis of *SELENOP*

Based on the cancer genomics data of cBioPortal (https://www.cbioportal.org/), we selected the mutation type and alteration frequency of TCGA pan-cancer studies for alteration analysis of *SELENOP* status in different tumor types.[23] Next, four survival rates were used to describe the difference in survival with and without the *SELENOP* alteration, including OS, PFS, DSS and disease-free survival (DFS).

Correlation of *SELENOP* Expression with TMB, MSI and MMR Genes Expression in Pan-Cancer

TMB is defined as the total number of somatic gene coding errors, base substitutions, and gene insertion or deletion errors detected per million bases, and is a potential biomarker that can predict the response to immunotherapy.[24] MSI associated with DNA MMR defects is another significant biomarker for prognostic and therapeutic outcomes. MSI refers to the phenomenon that new microsatellite alleles appear at a microsatellite locus in tumor due to the insertion or deletion of repeated units compared with normal tissue.[25] We calculated TMB scores by segmenting the total length of the exon using the Perl software. Similarly, MSI scores were calculated based on TCGA somatic mutation data in 33 tumor types. Next, we analyzed the association between *SELENOP* expression and these two biomarker scores.

MMR is helpful for the repair of DNA replication errors, and the loss of related gene functions can lead to the increased frequency of somatic mutations.[26] The correlation between *SELENOP* expression and MMR genes (MLH1, MSH2, MSH6, PMS2 and EPCAM) was assessed in 33 tumor types.

Immunity Correlation Analysis of *SELENOP* in Pan-Cancer

The relationship between *SELENOP* expression and immune infiltration was conducted using the TIMER (http://cistrome.org/TIMER/), which is a web server for comprehensive analysis of tumor immune infiltration.[27] *SELENOP* expression with the abundances of six immune infiltrates (B cells, CD4+ T cells, CD8+ T cells, Neutrophils, Macrophages and Dendritic cells) correlation analysis was performed. Moreover, the database can also quantify the effect of *SELENOP* expression on tumor purity.

In addition, we determined the correlation between cell markers of macrophage subtypes and *SELENOP* expression in 33 tumor types using the GEPIA. We selected the immune gene markers of tumor-associated macrophages (TAMs), M1 macrophages and M2 macrophages via the website of R&DSystems (https://www.rndsystems.com/cn/resources/cell-markers/immune-cells). These gene markers include *CD80, CD86, HLA-G, CD36, IL-6, NOS2, TGFβ, STAT6* and *IL-10*.

Tumor cells and their surrounding immune cells, tumor fibroblasts and vascular endothelial cells constitute the tumor microenvironment and determine the development of tumors. In order to evaluate the association between *SELENOP* expression and the infiltration level of stromal and immune cells in different types of tumor, we first determined stromal and immune scores by using ESTIMATE algorithm to quantitatively evaluate the infiltration level of stromal and immune cells. Then, we analyzed the association of *SELENOP* expression with stromal and immune scores using the R software.

PPI and Enrichment Analysis of *SELENOP*

We used GeneMANIA website (http://www.genemania.org) to construct Protein–Protein Interaction (PPI) network, including physical interaction, co-localization, protein domain, co-expressed and genetic interaction connections between *SELENOP* and related genes. To determine the biological process of *SELENOP* in 33 tumor types, Gene Set Enrichment Analysis (GSEA) was performed. We downloaded Gene Ontology (GO) from the GSEA website (https://www.gsea-msigdb.org/gsea/downloads.jsp) and used R software for enrichment analysis.

Statistical Analysis

We used the Wilcoxon rank-sum test to analyze differences in *SELENOP* expression between normal and tumor tissues. Correlation analysis was conducted using Spearman correlation method, including correlation of *SELENOP* expression with TMB, MSI and MMR gene expression, immune cells and tumor microenvironment in pan-cancer.

In survival analysis, Kaplan-Meier method and Log rank test were used to compare the association between different expression levels of *SELENOP* and patient prognosis. The relationship between *SELENOP* expression and OS, DSS and PFS in cancer patients was analyzed by univariate Cox proportional hazard model. All results analysis and visualization were performed using R software (version 3.6.1) and $P < 0.05$ were considered statistically significant.

Results
Pan-Cancer *SELENOP* Expression Level

First, the expression levels of *SELENOP* were analyzed in various blood cell types and non-tumor tissues by utilizing a combination of different datasets. Analysis of a combination of data from the Human Protein Atlas (HPA), GTEx and function annotation of the mammalian genome 5

(FANTOM5) revealed that *SELENOP* expression levels showed tissue enhancement, with the highest expression in the liver, followed by the intestine (Figure S1A). Human brain *SELENOP* expression profile was determined based on a combination of data from GTEx and FANTOM5. *SELENOP* can be expressed in ten main brain regions (all consensus normalized expression values >10), showing low regional specificity (Figure S1B). Because its corresponding protein is secreted into the blood, low cell type specificity was also present in 18 blood cell types and total peripheral blood mononuclear cells in the *SELENOP* expression analyzed based on the data from HPA/Monaco/Schmiedel (Figure S1C).

Next, we explored the expression patterns of *SELENOP* in TCGA pan-cancer data. The results showed that *SELENOP* expression was significantly higher in normal tissues, including BLCA (bladder urothelial carcinoma), BRCA (breast invasive carcinoma), CHOL (cholangiocarcinoma), COAD (colon adenocarcinoma), ESCA (esophageal carcinoma), HNSC (head and neck squamous cell carcinoma), KICH (kidney chromophobe), KIRC (kidney clear cell carcinoma), KIRP (kidney papillary cell carcinoma), LIHC (liver hepatocellular

carcinoma), LUAD, LUSC (lung squamous cell carcinoma), PCPG (pheochromocytoma and paraganglioma), PRAD (prostate adenocarcinoma), READ (rectum adenocarcinoma), STAD (stomach adenocarcinoma), THCA (thyroid carcinoma) and UCEC, compared to that in the corresponding tumor tissues (Figure 1A). Considering the absence or a limited number of normal tissues in some cancers, the GEPIA2 was used to analyze *SELENOP* expression in several cancer types in the GTEx database. Similarly, a lower *SELENOP* expression was found in OV (ovarian serous cystadenocarcinoma), SKCM (skin cutaneous melanoma) and UCS (uterine carcinosarcoma) in the tumor groups (Figure 1B). However, *SELENOP* expression in the tumor tissues was significantly higher in DLBC (diffuse large B-cell lymphoma), LAML (acute myeloid leukemia) and LGG (brain lower grade glioma) than in normal tissues.

The expression pattern of SeP at a protein level was investigated in the CPTAC dataset. The results suggested that SeP expression in the normal tissues was significantly higher than that in the tumor tissues, including clear cell RCC, breast cancer, ovarian cancer, colon cancer, LUAD and UCEC (Figure 1C).
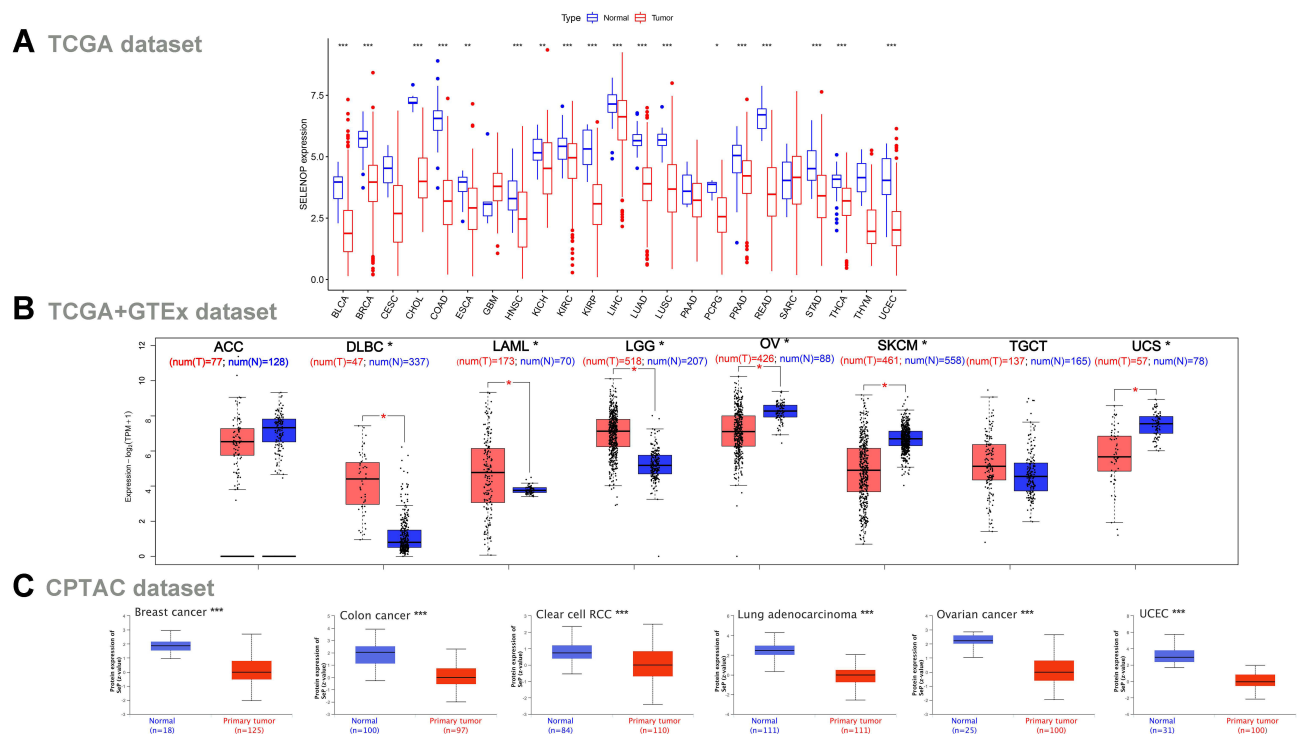

Figure 1 Expression level of *SELENOP* in different tumors. (**A**) *SELENOP* expression in 33 tumor types (based on TCGA database). (**B**) The corresponding normal tissues of the GTEx database were included as controls, compared with ACC, DLBC, LAML, LGG, OV, SKCM, TGCT, UCS tumor tissues in TCGA database. (**C**) The expression level of SeP total protein in 6 tumors (based on CPTAC dataset). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.
Abbreviations: ACC, adrenocortical cancer; DLBC, diffuse large B-cell lymphoma; LAML, acute myeloid leukemia; LGG, brain lower grade glioma; OV, ovarian serous cystadenocarcinoma; SKCM, skin cutaneous melanoma; TGCT, testicular germ cell tumor; UCS, uterine carcinosarcoma.

Pan-Cancer Multifaceted Prognostic Potential and Genetic Alteration of *SELENOP*

TCGA dataset was used to evaluate the pan-cancer correlation of *SELENOP* expression with prognosis values. The OS, PFS and DSS results were obtained using a Cox proportional-hazards model (Figure 2). Notably, the forest plots revealed that *SELENOP* expression was significantly correlated with five cancer types, including ACC (adrenocortical cancer), KIRC, LGG, LUAD and UCEC. Among them, *SELENOP* expression had a protective role in the prognosis of three cancer types, including ACC (OS HR = 0.712, $P = 0.045$; PFS HR = 0.771, $P = 0.039$), KIRC (OS HR = 0.630, $P < 0.001$; PFS HR = 0.669, $P < 0.001$; DSS

HR = 0.562, $P < 0.001$), and LUAD (OS HR = 0.805, $P < 0.001$; PFS HR = 0.867, $P = 0.009$). In addition, *SELENOP* had a detrimental role in the other two cancer types, including LGG (OS HR = 1.303, $P = 0.003$; PFS HR = 1.238, $P = 0.004$; DSS HR = 1.365, $P < 0.001$) and UCEC (OS HR = 1.340, $P = 0.002$; PFS HR = 1.197, $P = 0.016$; DSS HR = 1.278, $P = 0.020$).

The KM curves for OS, PFS and DSS in patients with different types of tumor are shown in Figure 3 and S2. For the OS, highly expressed *SELENOP* was linked to poor prognosis for LGG (Figure 3B; $P = 0.001$) and UCEC (Figure 3D; $P = 0.002$). A low expression level of *SELENOP* was related to a worse clinical outcome for KIRC (Figure 3A; $P < 0.001$) and LUAD (Figure 3C; $P = 0.005$). Moreover, PFS and DSS data analysis (Figure S2) revealed associations between high
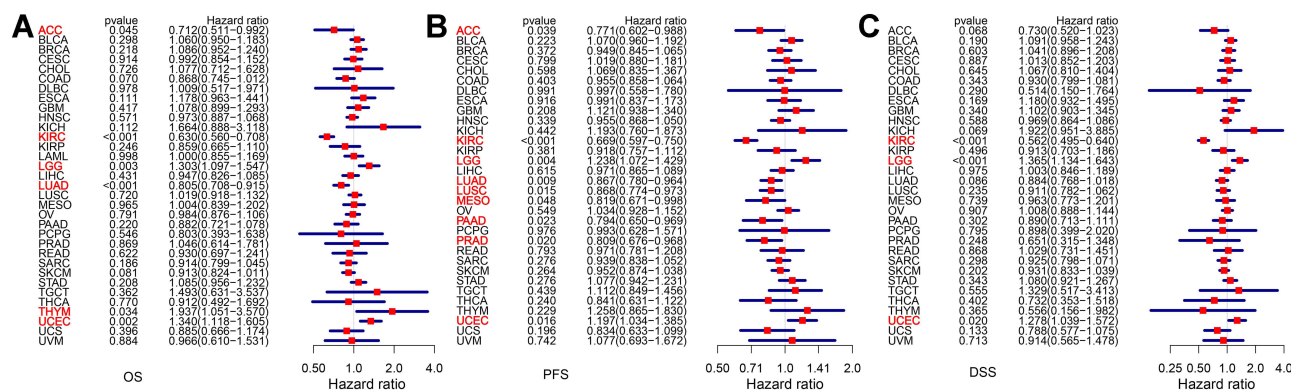

Figure 2 Association between *SELENOP* expression and OS, PFS and DSS. (**A**) Forest plot of OS associations in 33 types of tumor. (**B**) Forest plot of PFS associations in 33 types of tumor. (**C**) Forest plot of DSS associations in 33 types of tumor.
Abbreviations: OS, overall survival; PFS, progression-free survival; DSS, disease-specific survival.

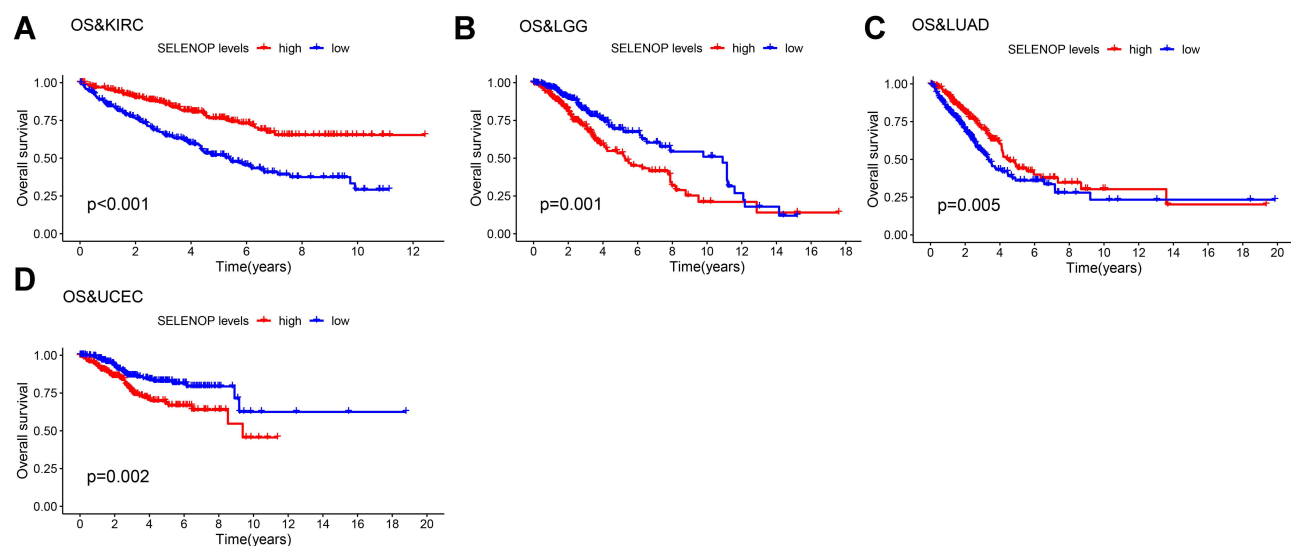**Figure 3** Kaplan–Meier analysis of the association between *SELENOP* expression and OS. (**A**) Kaplan–Meier plot of high and low *SELENOP* expression in KIRC patients. (**B**) and in LGG patients. (**C**) and in LUAD patients. (**D**) and in UCEC patients.
Abbreviations: KIRC, kidney clear cell carcinoma; LGG, brain lower grade glioma; LUAD, lung adenocarcinoma; UCEC, uterine corpus endometrioid carcinoma.

SELENOP expression and poor prognosis for LGG and UCEC. However, *SELENOP* expression had the opposite relationship in KIRC. Analysis results for *SELENOP* in TCGA survival data confirmed its multifaceted prognostic potential that depends on the tumor type.

The genetic alteration of *SELENOP* was investigated in patients with different tumors using the cBioPortal database in order to determine if it plays a role in prognosis. The results suggested that amplification was the primary alteration type in most cancer cases, such as in LUAC, LUAD, ESCA and STAD (Figure 4A). In addition, *SELENOP* mutation frequencies were highest in SKCM, followed by UCEC. Next, we explored whether genetic alteration of *SELENOP* and clinical prognosis outcomes were related. Compared to the altered group of UCEC cases, the unaltered group was related to a better prognosis for DSS ($P = 0.014$) and PFS ($P = 0.026$), but not for OS ($P = 0.115$) and DFS ($P = 0.170$; Figure 4B–E).

Relationships Between *SELENOP* Expression and MSI, TMB and MMR Genes

The relationship between MSI, TMB and MMR genes and *SELENOP* expression was analyzed to further explore the role of *SELENOP* in tumorigenesis. There was a significant negative correlation with *SELENOP* expression and MSI in 12 tumor types, such as BRCA, KICH, LUAD, OV, SKCM and STAD (Figure 5A). Except for LAML, which had a positive correlation with *SELENOP* expression and TMB, the other 14 cancer types, including BRCA, LGG, LUAD, PAAD (pancreatic adenocarcinoma), SKCM, STAD and UCEC, showed a significant negative correlation (Figure 5B). In addition, except in ESCA, GBM (glioblastoma multiforme) and LGG, *SELENOP* expression was positively correlated with MMR genes in most tumor types (Figure 5C).

Relationships Between *SELENOP* Expression and Immune Infiltration and Tumor Microenvironment

The activity pattern of immune cells affects tumor development and patient survival times. Therefore, immune infiltration analysis based on the TIMER database was performed to examine the relationship between *SELENOP* expression and infiltration levels in pancancer. Infiltration level was calculated using the score for the following six types of immune cells: B cells,
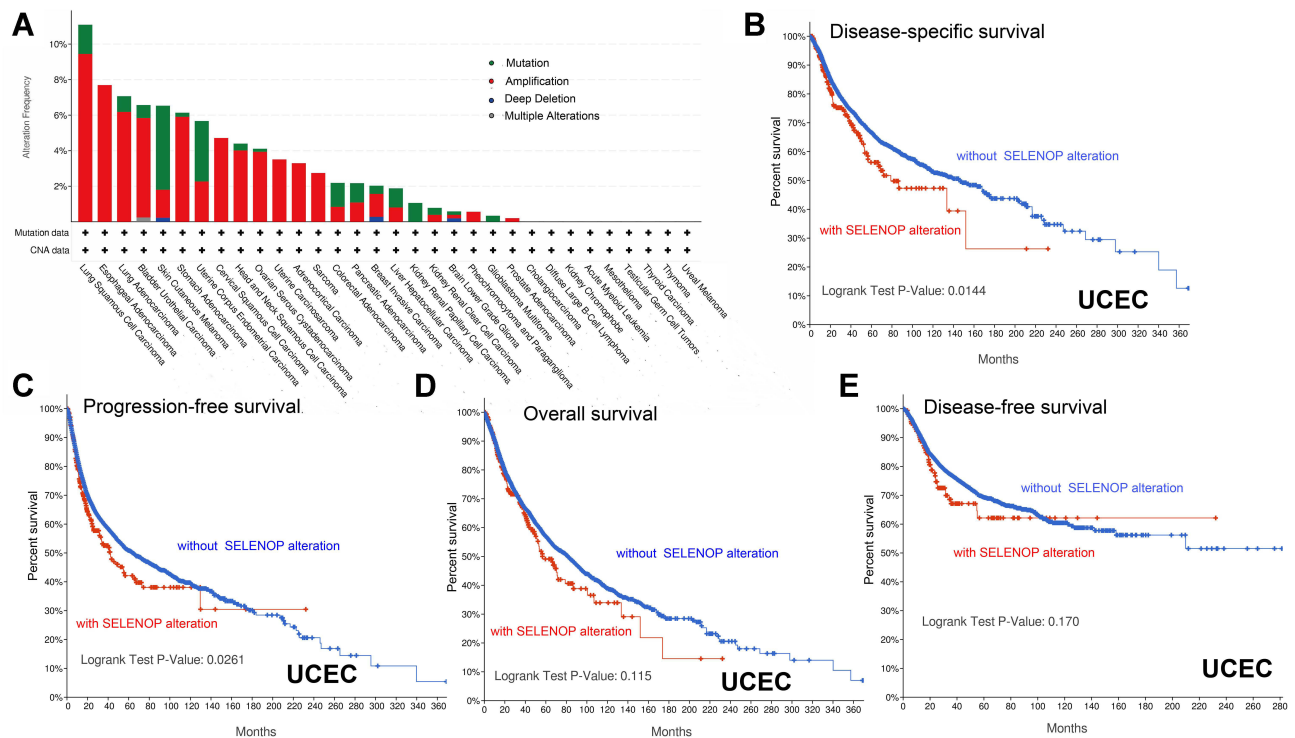
Figure 4 Mutation feature of *SELENOP* in different tumor types of TCGA. (**A**) The genetic alteration type and frequency of *SELENOP* in various tumors (based on the cBioPortal tool). (**B**) The potential correlation between mutation status and disease-specific survival of UCEC. (**C**) and progression-free survival of UCEC. (**D**) and overall survival of UCEC. (**E**) disease-free survival of UCEC.
Abbreviation: UCEC, uterine corpus endometrioid carcinoma.

Figure 5 Associations between *SELENOP* expression and microsatellite instability (MSI), tumor mutational burden (TMB) and mismatch repair (MMR) in 33 tumor types. (**A**) Results of correlation analysis between *SELENOP* expression in 33 tumor types and MSI. (**B**) and TMB. The P-value is supplied. The correlation coefficient values of +0.4 and − 0.4 are marked. (**C*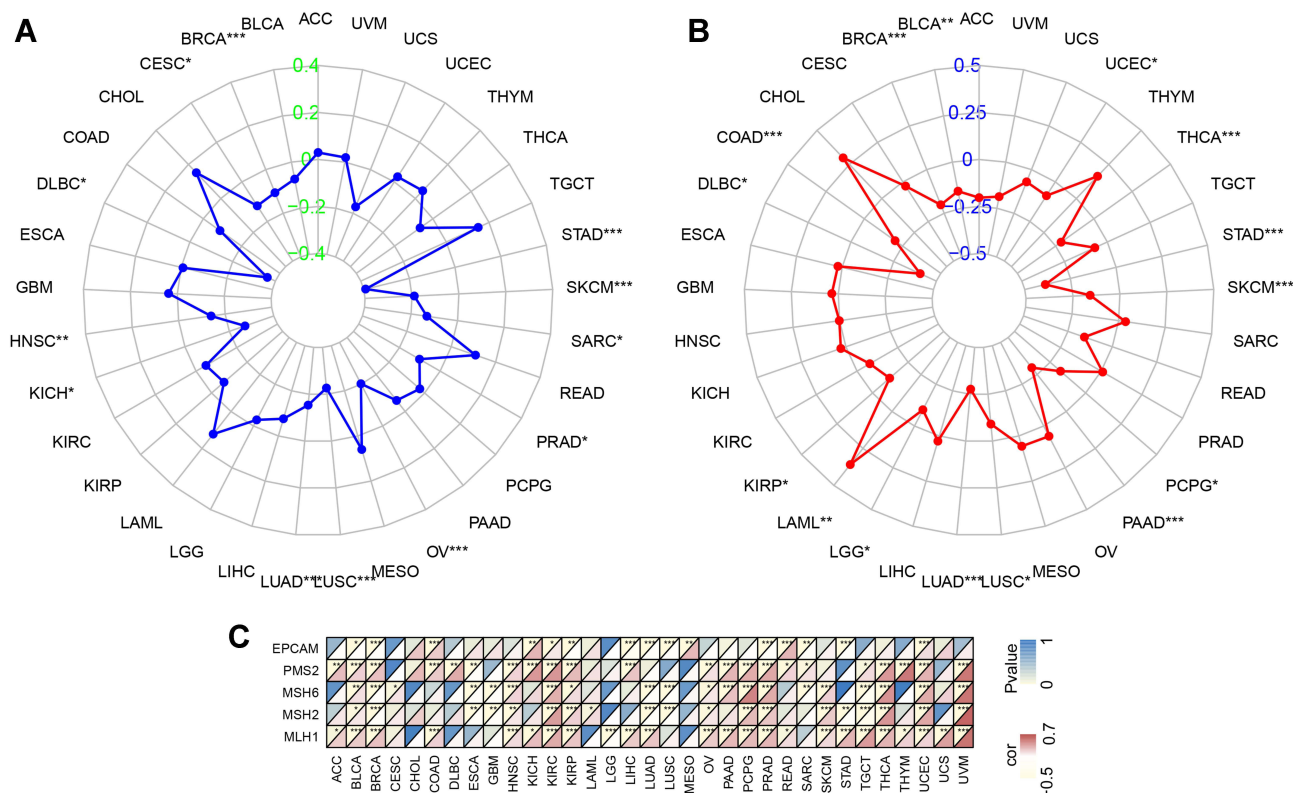*) and five MMR genes. The top left triangle represents the *P*-value, and the bottom right triangle represents the correlation coefficient. *P < 0.05, **P < 0.01 and ***P < 0.001.

CD4+ T cells, CD8+ T cells, neutrophils, macrophages and dendritic cells.

There were four types of cancer whose *SELENOP* expression was associated with the infiltration levels of all six immune cell types (Figure 6). *SELENOP* expression had a significant negative correlation with tumor purity, except in KIRC (r = −0.034, P < 0.0001). The results also suggested that increased infiltration of six immune cell types was associated with increased *SELENOP* expression in the following cancers: KIRC, LGG, LUAD and SKCM. However, *SELENOP* expression had a strong positive correlation with macrophage infiltration levels in four tumor types (r > 0.4, P < 0.0001). To further examine the relationship between macrophage infiltration and *SELENOP*, the correlation analysis between cell markers of macrophage subtypes and *SELENOP* expression was conducted in GEPIA. Immune marker genes for macrophage subtypes included tumor-associated macrophages (*CD80, CD86* and *HLA-G*), M1 macrophages (*CD36, IL-6* and *NOS2*), and M2 macrophages (*TGFβ, STAT6* and *IL-*

10). The results revealed that *SELENOP* expression was positively correlated with most macrophage immune marker genes in pan-cancer (Table 2). However, there was no evidence to support the regulation of macrophage polarization via *SELENOP* expression in any type of cancer.

Furthermore, the effect of pan-cancer *SELENOP* expression using the R package estimate was determined in the immune microenvironment. *SELENOP* expression had a significant positive correlation with stromal and immune scores in TGCT, SKCM, SARC, PCPG, KIRP, PAAD and GBM (Figure 7). The six tumors with the highest correlation coefficients between *SELENOP* expression and stromal scores were TGCT (R = 0.61), SKCM (R = 0.55), SARC (sarcoma) (R = 0.52), PCPG (R = 0.51), KIRP (R = 0.46) and PAAD (R = 0.43). The top six tumors whose *SELENOP* expression was most significantly positively correlated with immune scores were SARC (R = 0.43), SKCM (R = 0.40), PAAD (R = 0.40), GBM (R = 0.37), PCPG (R = 0.37) and KIRP (R = 0.32) (all P < 0.05).
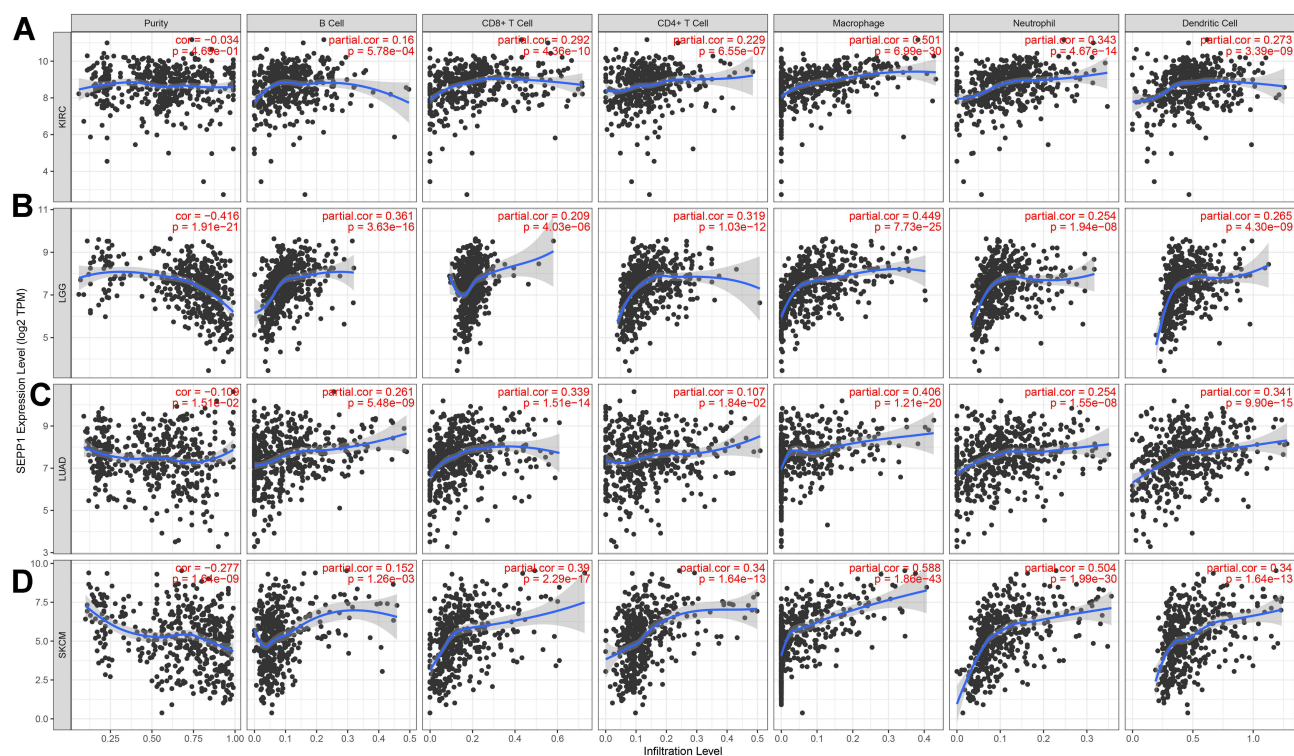
Figure 6 Associations between *SELENOP* expression and tumor immune infiltration. (**A**) Correlation analysis between expression levels of *SELENOP* and immune cell infiltration in KIRC. (**B**) and in LGG. (**C**) and in LUAD. (**D**) and in SKCM.
Abbreviations: KIRC, kidney clear cell carcinoma; LGG, brain lower grade glioma; LUAD, lung adenocarcinoma; SKCM, skin cutaneous melanoma.

SELENOP PPI Network and GSEA in Pan-Cancer

To further investigate the roles for *SELENOP* in the development of 33 tumor types, a PPI network analysis and GSEA of *SELENOP* were conducted. Using the GeneMANIA online tool, a strong physical interaction was revealed between *SELENOP* and mesenchyme homeobox 2 (*MEOX2*; Figure 8). *MEOX2* is expressed in vascular endothelial cells and it inhibits their proliferation.[28] This potential function is consistent with the pathway enrichment analysis in LGG and UCEC. A common feature of the GO enrichment term indicated that *SELENOP* negatively regulated vascular endothelial cell proliferation in LGG and UCEC (Figure 9A). Similarly, *SELENOP* expression was negatively correlated with cell proliferation, differentiation, and adhesion in KIRC, LUAD, STAD, BRCA, SARC and THCA, including epidermal cell differentiation, keratinization and epidermis development (Figure 9B and S3A). In contrast, in COAD, PCPG, SKCM, OV, PAAD and UVM, the process of upregulation was related to the immune function, including T cell activation, B cell-mediated immunity, adaptive immune response and

immune response regulation cell surface receptor signaling pathways (Figure 9C and S3B).

Discussion

The protective effect of selenoprotein family is usually attributed to its antioxidant properties in tumorigenesis. However, little research has been done on selenoproteins in tumor development, such as *SELENOP*. Due to the complexity of the mechanism, the relationship between selenoproteins and cancer should be analyzed from multiple perspectives, including DNA stability, immune responses and related signaling pathways.[29–31] Thus, the present study attempted to explore the pan-cancer role of *SELENOP* in terms of tissue specificity, immune microenvironment and signaling pathways.

After intestinal absorption, various Se compounds reach the liver and are incorporated into selenoproteins, including SeP (Figure 10).[32] Plasma SeP serves as a transport protein to supply Se to target tissues, such as the brain, kidney and testis. Many studies have revealed that SeP uptake in the brain and testis is mediated by Lrp8 (apolipoprotein E receptor 2, ApoER2), a member of the low-density lipoprotein receptor-related protein

Table 2 Correlation Between *SELENOP* and Macrophage Gene Markers Based on GEPIA Online Tool, Including TAM and M1 and M2 Macrophages

| Tumors | TAM | | | | | | | | M1 Macrophage | | | | M2 Macrophage | | | | | |
| | CD80 | | CD86 | | HLA-G | | CD36 | | IL-6 | | NOS2 | | TGFβ | | STAT6 | | IL-10 | |
	R	P	R	P	R	P	R	P	R	P	R	P	R	P	R	P	R	P
ACC	0.17	0.14	0.3	*	0.14	0.22	0.44	***	0.23	*	0.21	0.061	0.26	*	0.45	***	0.37	**
BLCA	0.11	*	0.22	***	0.11	*	0.4	***	0.084	0.093	0.17	**	0.066	0.19	0.23	***	0.21	***
BRCA	0.049	0.11	0.16	***	-0.099	*	0.39	***	0.085	*	0.033	0.28	0.12	***	0.31	***	0.24	*
CESC	0.12	*	0.15	*	-0.044	0.44	0.23	***	-0.18	0.67	0.28	***	-0.054	0.34	0.35	***	0.1	0.067
CHOL	-0.3	0.076	-0.22	0.2	-0.13	0.44	0.062	0.72	0.075	0.67	0.21	0.22	-0.2	0.23	0.29	0.09	-0.16	0.34
COAD	0.24	***	0.29	***	0.15	*	0.36	***	0.2	*	0.029	0.63	0.2	***	0.15	*	0.34	***
DLBC	0.18	0.22	0.2	0.19	0.083	0.58	0.2	0.19	-0.11	0.48	-0.038	0.8	0.22	0.14	0.25	0.086	-0.15	0.33
ESCA	0.036	0.63	0.032	0.67	0.027	0.72	0.28	***	0.0066	0.93	0.23	*	-0.045	0.54	0.16	*	0.0036	0.96
GBM	0.2	*	0.42	***	-0.028	0.73	0.22	*	0.032	0.69	0.044	0.58	0.15	0.055	0.34	***	0.41	***
HNSC	0.25	***	0.31	***	-0.032	0.47	0.32	***	0.09	*	0.31	***	0.015	0.73	0.27	***	0.27	***
KICH	0.31	*	0.31	*	0.11	0.37	0.31	*	-0.031	0.81	0.18	0.15	0.23	0.068	0.37	*	0.28	*
KIRC	0.2	***	0.36	***	0.042	0.34	0.49	***	-0.11	*	0.42	***	0.057	0.19	0.35	***	0.4	***
KIRP	0.48	***	0.54	***	0.19	**	0.52	***	0.29	***	0.25	***	0.28	***	0.25	***	0.6	***
LAML	0.31	***	-0.18	*	-0.088	0.25	-0.1	0.17	0.1	0.18	-0.17	*	-0.11	0.16	-0.082	0.29	-0.035	0.65
LGG	0.15	**	0.47	***	0.064	0.15	0.0086	0.85	0.12	*	0.053	0.23	0.28	***	0.32	***	0.28	***
LIHC	-0.087	0.094	-0.085	0.1	0.02	0.71	0.46	***	-0.029	0.57	0.28	***	-0.34	***	0.26	***	0.058	0.27
LUAD	0.3	***	0.34	***	0.13	*	0.51	***	-0.04	0.38	0.12	*	0.14	*	0.32	***	0.44	***
LUSC	0.15	**	0.33	***	0.11	*	0.5	***	0.08	0.078	0.2	***	0.095	*	0.14	*	0.35	***
MESO	0.18	0.1	0.21	*	-0.21	0.052	0.32	*	0.12	0.26	0.3	*	0.15	0.18	0.071	0.51	0.3	*
OV	0.17	**	0.22	***	0.11	*	0.24	***	0.097	*	0.22	***	0.22	***	0.19	***	0.25	***
PAAD	0.19	*	0.43	***	-0.18	*	0.59	***	0.27	**	0.2	*	-0.15	*	0.065	0.39	0.4	***
PCPG	0.4	***	0.57	***	0.16	*	0.48	***	0.38	***	0.11	0.14	0.32	***	0.27	*	0.61	***
PRAD	0.23	***	0.33	***	0.0078	0.86	0.59	***	0.14	*	0.12	*	0.0012	0.98	0.38	***	0.33	***
READ	0.25	*	0.29	*	0.16	0.13	0.33	*	0.077	0.46	0.22	*	0.11	0.3	-0.018	0.86	0.28	*
SARC	0.37	***	0.56	***	0.21	**	0.6	***	0.31	***	0.24	***	0.18	*	0.12	*	0.56	***
SKCM	0.54	***	0.61	***	-0.025	0.6	0.53	***	0.22	***	0.11	*	0.3	***	0.15	*	0.51	***
STAD	0.19	**	0.31	***	0.036	0.47	0.59	***	0.12	*	0.038	0.44	0.29	***	0.3	***	0.33	***
TGCT	-0.071	0.41	0.025	0.77	-0.14	0.11	0.58	***	-0.34	***	0.46	***	0.51	***	0.6	***	0.15	0.082
THCA	0.17	***	0.23	***	0.071	0.11	0.27	***	0.24	***	0.32	***	0.16	**	0.51	***	0.34	***
THYM	0.34	**	0.55	***	0.24	*	0.47	***	0.39	***	0.21	*	0.32	**	0.57	***	0.67	***
UCEC	0.17	*	0.11	0.15	0.11	0.15	0.26	**	0.064	0.4	0.15	0.055	-0.00051	0.99	0.37	***	0.12	0.1
UCS	0.54	***	0.63	***	0.28	*	0.33	*	0.29	*	0.25	0.057	0.28	*	0.37	*	0.48	**
UVM	0.45	***	0.62	***	0.16	0.17	0.37	***	0.36	*	0.092	0.42	0.22	*	0.42	***	0.65	***

Notes: *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$.
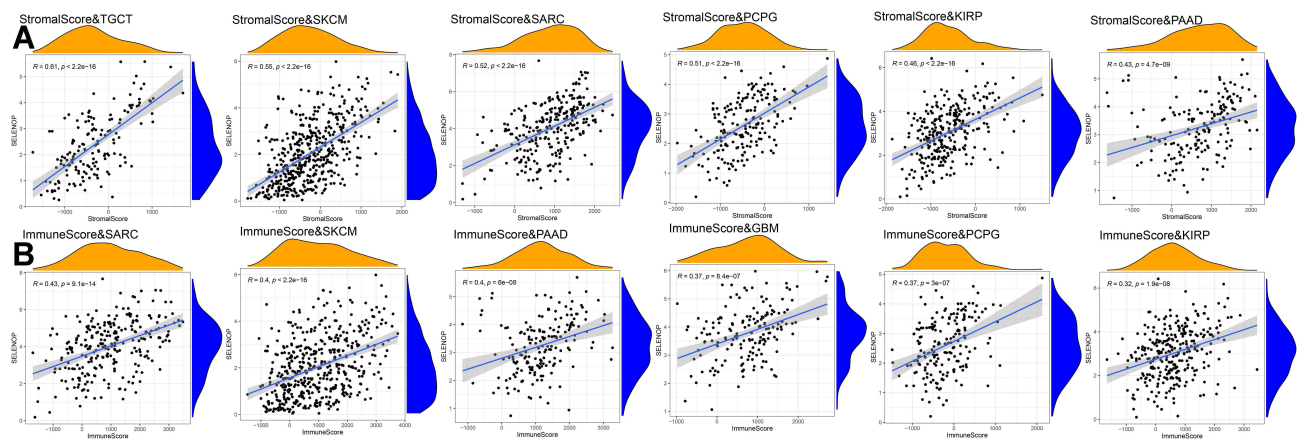**Abbreviation:** TAM, Tumor-Associated Macrophage.

Figure 7 Six tumors with the highest correlation coefficients between *SELENOP* expression and the tumor microenvironment. (**A**) Correlation between *SELENOP* and stromal scores in TGCT, SKCM, SARC, PCPG, KIRP and PAAD. (**B**) Correlation between *SELENOP* and immune scores in SARC, SKCM, PAAD, GBM, PCPG and KIRP.
Abbreviations: TGCT, testicular germ cell tumor; SKCM, skin cutaneous melanoma; SARC, sarcoma; PCPG, pheochromocytoma and paraganglioma; KIRP, kidney papillary cell carcinoma; PAAD, pancreatic adenocarcinoma; GBM, glioblastoma multiforme.
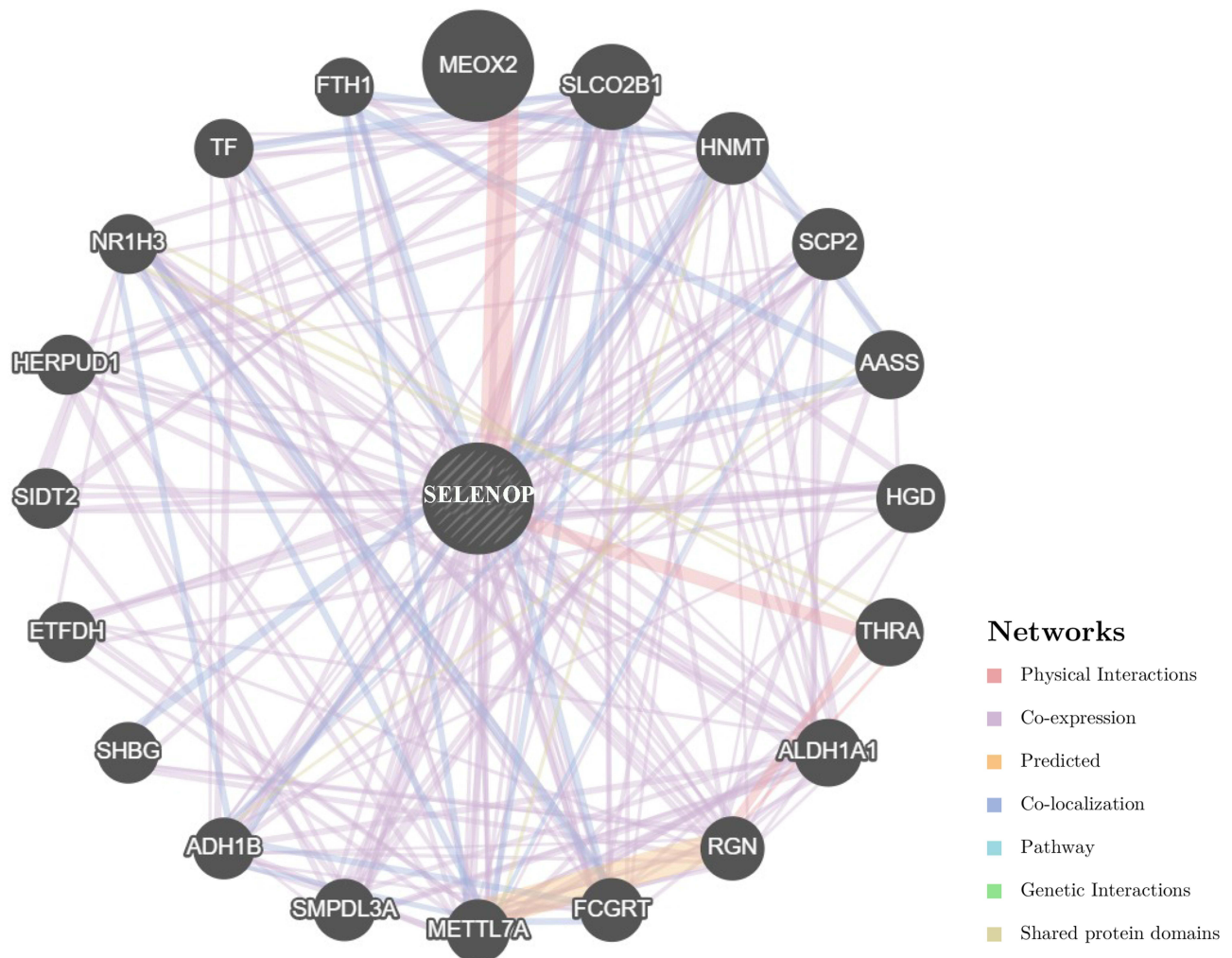

Figure 8 PPI network for *SELENOP* based on GeneMANIA online tool. Different colors of the network edge indicate the bioinformatics methods applied: physical interaction, co-expression, predicted, colocalization, pathway, genetic interaction, and shared protein domains.
Abbreviation: PPI, protein–protein interaction.

Figure 9 GO functional annotation of GSEA of *SELENOP* in various tumor types. (**A**) A common feature in LGG and UCEC was that *SELENOP* negatively regulated vascular endothelial cell proliferation. (**B**) *SELENOP* expression was negatively correlated with epidermal cell differentiation, keratinization and epidermis development in KIRC, LUAD and STAD. (**C**) In COAD, PCPG and SKCM, the process of upregulation was related to immune function, including T cell activation, B cell mediated immunity, adaptive immune response and immune response regulation cell surface receptor signaling pathways.

Abbreviations: COAD, colon adenocarcinoma; STAD, stomach adenocarcinoma; KIRC, kidney clear cell carcinoma; LGG, brain lower grade glioma; LUAD, lung adenocarcinoma; SKCM, skin cutaneous melanoma; UCEC, uterine corpus endometrioid carcinoma; PCPG, pheochromocytoma and paraganglioma.

family.[33,34] In addition to Lrp8, SeP can also bind the Lrp2 (megalin) receptor in the kidney.[35] Some tissues that express *SELENOP* but do not express *Lrp8* and *Lrp2* may exert the physiological effects of *SELENOP* through mechanisms that remain unclear.

Due to its transport function, *SELENOP* expression was decreased in many cancer tissues compared to normal tissues, such as in COAD, KICH, KIRC, KIRP, LIHC, LUAD, PRAD, SKCM, THCA and UCEC (Figure 1A). In contrast, *SELENOP* expression was upregulated in tumor tissues, including DLBC, LAML and LGG (Figure 1B). *SELENOP* expression downregulation has been demonstrated in several

types of tumor, including hepatocellular carcinomas, gastric adenocarcinomas, colorectal cancer, non-small cell lung cancer, renal cancer and prostate cancer.[17,36–40]

Survival analysis in TCGA database showed that *SELENOP* expression was associated with a better prognosis in ACC, KIRC, LUAD and PRAD, and a poorer prognosis in LGG and UCEC (Figure 2). Higher alteration frequency of *SELENOP* was present in SKCM and UCEC compared to other cancers (Figure 4A). In addition, the association between *SELENOP* expression and prognosis may be related to mutation in UCEC, which has a detrimental impact on prognosis (Figure 4B–C).

It may not be surprising that the absence of *SELENOP*'s antioxidant protection promotes the development of some cancers.[14,18] However, it cannot be ruled out that the relationship between SeP and the two receptors (Lrp8 and Lrp2) may regulate the downstream oncogenic signaling pathway.[41] For example, *apoER2* (*Lrp8*) knockdown of the downstream component of Reelin (a key regulator of neuronal migration) inhibits cell migration and invasion in pancreatic cancer.[42] It is worth noting that *SELENOP* plays an important role in the brain. *SELENOP* mRNA is expressed in neurons and glial cells.[43] In addition, SeP and apoER2 may supply Se to the brain at the blood-brain barrier.[34] Most researchers have focused on *SELENOP* and neurodegenerative diseases, and there has been no investigation of the relationship between *SELENOP* and brain cancer.[44,45] The present study found that *SELENOP* may be a risk factor in LGG, but the SeP-apoER2 interaction in tumorigenesis remains unclear.

SELENOP can also affect immune cell recruitment. Se deficiency has been shown to weaken the immune response of tumor cells.[46] This condition is usually accompanied by changes in cytokines, such as *COX-2, TNF-α,* and *TGF-β.*[47] Likewise, several studies have confirmed that certain cytokines are regulated by *SELENOP*, including *TNF-α*, hepatocyte growth factor, vascular endothelial growth factor (VEGF), and *IL-6.*[48,49] Although the specific mechanism remains unclear, Bosschaerts et al have reported that *IL-10* promotes *SELENOP* expression.[50] In studies related to the inflammatory response of *SELENOP*, it was highly expressed in alternatively activated M2 macrophage phenotype and involved in the conversion from classical M1 to M2 macrophage and in colitis-associated cancer. The tumorigenesis promotion may have occurred due to macrophage polarization in *SELENOP* heterozygous mice.[19,50]

The present results showed that *SELENOP* is associated with the infiltration level of six immune cell types, in which *SELENOP* had a strong correlation with macrophages in some cancer types (Figure 6). This may have been caused by the heterogeneity of immune cell recruitment in the tumor microenvironment. The relationship between *SELENOP* expression and immune marker genes of macrophage subtypes, such as *CD80, CD86, HLA-G, CD36, IL-6, NOS2, TGFβ, STAT6* and *IL-10*, was further analyzed (Table 2). Macrophage polarization was not present in 33 tumor types. Therefore, the oncogenic effect of *SELENOP* and macrophage polarization

may occur in inflammatory tumorigenesis, while in most other tumors, *SELENOP* may exhibit anti-carcinogenic properties.[51]

The potential association between *SELENOP* and immune function was verified using pathway enrichment analysis in COAD, PCPG, SKCM, OV, PAAD and UVM (Figure 9C and S3B). Speckmann et al have reported that *SELENOP* secreted in the small intestine was involved in regulating the activation and differentiation of immune cells and maintained the local immune defense in the intestine.[52] In addition, *SELENOP* may regulate cell proliferation, migration, adhesion and angiogenesis in some cancers (Figure 9B and S3A). Selenoproteins can inhibit tumor cell metastasis.[7] For example, *GPX2* and *GPX3* negatively regulated cell migration and invasion, while *TXNRD1* knockdown reduced *VEGF* and thus inhibited angiogenesis.[53–56]

The present study represented the first pan-cancer analysis of *SELENOP*. Study results indicated a close relationship between *SELENOP* and tumorigenesis using
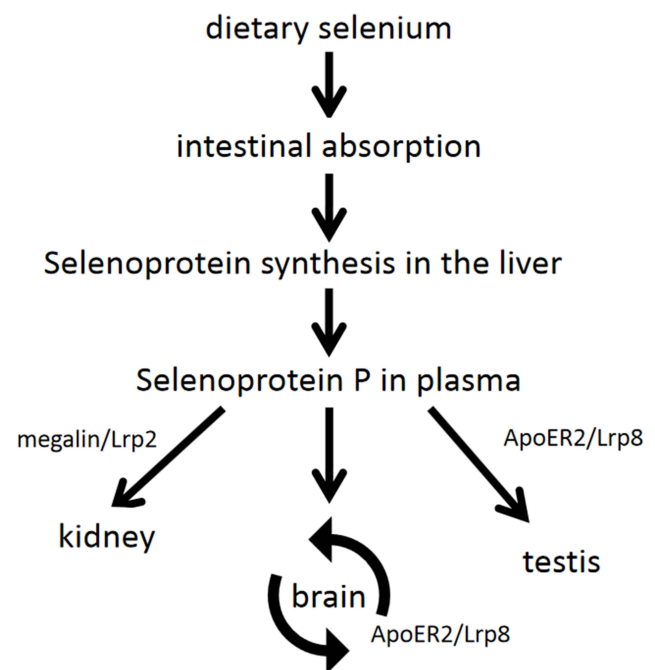

Figure 10 Summary of the transport function of SeP. Dietary Se is absorbed through the small intestine, and various Se compounds synthesize selenoprotein in the liver via circulation of portal vein, including SeP. Plasma SeP preferentially transports Se to various target tissues, such as the brain, kidney and testis. SeP transport in the brain is complicated because Se passes through multiple cell membranes before eventually reaching neurons. The neuronal SeP synthesis and ApoER2/Lrp8-mediated SeP reuptake in the brain are called the SeP cycle. Testicular function is also dependent on ApoER2/Lrp8-mediated SeP uptake. Megalin/Lrp2 is expressed in renal tubular epithelium and is involved in the reabsorption of SeP from glomerular filtrate.
Abbreviations: SeP, Selenoprotein P; Se, Selenium; ApoER2, apolipoprotein E receptor 2.

tissue-specific, immune function and pathway enrichment analyses. *SELENOP* expression was also shown to be downregulated and associated with a more favorable prognosis in most tumor tissues. A series of analyses indicated that *SELENOP* had anti-carcinogenic properties and a positive prognostic potential in most cancer types. In addition to *SELENOP's* antioxidant properties, the present study focused on its the multifaceted pan-cancer properties in immunity, cell proliferation, differentiation, invasion and angiogenesis. Although the current exploration of pan-cancer *SELENOP* mRNA was performed using bioinformatics, further experimental studies should focus on the specific *SELENOP* function in each cancer type. The present study had some limitations. First, it almost completely relied on mRNA levels. Second, the relationship among Se, SeP, *SELENOP* mRNA and immune status in cancers requires further study. Besides, whether the specific receptors and both immune and signaling pathways of *SELENOP* can have multiple effects in different cancer types remains an open question.

Conclusion

To the best of our knowledge, this is the first pan-cancer analysis of *SELENOP* to investigate its characteristics in tissue-specific expression, survival prognosis, TMB, MSI, immune function and pathway enrichment. Based on the present study results, *SELENOP* may be tissue-specific in cancers, such as the brain, kidney, lung, gastrointestinal and reproductive system tumors. In addition to its known antioxidant activity, the molecular mechanism of *SELENOP* in tumor immunity and metastasis requires a further investigation.

Data Sharing Statement

The data supporting the results of the study are available from the TCGA database (https://portal.gdc.cancer.gov/).

Disclosure

The authors declare that they have no conflict of interest.

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