A pan-cancer exploration of kinesin family member 20A (KIF20A)'s oncogenic activity in human tumors

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Research Article

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Abstract

Background: Increasing evidence has revealed that kinesin family member 20A (KIF20A) is highly expressed in a variety of cancers and is related to the occurrence and prognosis of cancer. However, a pan-cancer analysis has not been performed.

Methods and results: Based on data from The Cancer Genome Atlas (TCGA), Genotype-Tissue Expression (GTEx), Clinical Proteomic Tumor Analysis Consortium (CPTAC) and Human Protein Atlas (HPA) databases, we clarified the expression of KIF20A in 33 tumor types using a series of bioinformatics analyses. KIF20A is highly expressed in the majority of malignancies, and there were distinct connections between KIF20A expression and pathological stage and prognosis in tumor patients. KIF20A overexpression was associated with poor overall survival (OS) and disease-free survival (DFS) in patients with certain cancers, such as adrenocortical carcinoma, kidney renal clear cell carcinoma and brain lower grade glioma. The associations of KIF20A expression with immune cell infiltration, including the levels of infiltrating B cells, T cells, and dendritic cells, varied among tumors. Moreover, we found a positive association between KIF20A expression and cancer-associated fibroblast infiltration in patients with esophageal carcinoma (ESCA), mesothelioma (MESO) and thyroid carcinoma (THCA). In addition, we identified five genes, KIF2C, KIF23, CDC25, CCNB1 and DLGAP5, whose expression was positively related to KIF20A expression.

Conclusions: This pan-cancer study provides a comprehensive understanding of KIF20A's oncogenic functions in a variety of human tumors.

Background

Kinesin family member 20A (KIF20A), also known as Rabkinesin-6 or mitotic kinesin-like protein 2, is a protein comprising eight hundred and ninety amino acids that possesses one highly conserved kinesin-motor domain, and KIF20A belongs to the kinesin-like protein family [1, 2]. The human KIF20A gene is located on chromosome 5q31.2 and shows tissue-specific expression [3]. KIF20A expression is especially associated with the mitotic state of proliferating cells, including the stem/progenitor cells of different tissues [4, 5].

Studies have reported that KIF20A is overexpressed in a series of cancers, such as lung cancer [6, 7], hepatocellular carcinomas [8, 9], bladder cancer [10], gastric cancer [11, 12], pancreatic cancer [13], cervical squamous cell carcinoma [14], glioma [15, 16], renal cell carcinoma [17], breast cancer [18, 19], ovarian clear-cell carcinoma [20] and medulloblastoma [21]. It has been elucidated that KIF20A plays a pivotal role in tumorigenesis by participating in cell proliferation, differentiation, migration, invasiveness, neurogenesis and angiogenesis [22–24]. Moreover, some researchers have found that high KIF20A expression may enhance resistance to chemotherapy in breast cancer [25], prostate cancer [26], glioma [16] and colorectal cancer [27]. A growing number of studies indicate that high expression of KIF20A is correlated with worse prognosis and adverse clinicopathological features of patients with different types

of tumors [23, 28–30]. The antitumor effect of a KIF20-derived peptide vaccine, as a novel immunotherapy agent, has been explored in several phase I/II clinical trials. However, no data are available about the role of KIF20A across cancers [31, 32].

In the present study, for the first time, we used the ONCOMINE, TIMER2, PrognoScan, Gene Expression Profiling Interactive Analysis 2 (GEPIA2), and Kaplan–Meier Plotter databases to conduct a pan-cancer analysis of KIF20A. In addition to assessing KIF20A gene expression and genetic alterations, we also explored the potential relationships between KIF20A expression and survival status and immune cell infiltration to clarify the molecular mechanisms of KIF20A in the pathogenesis of different cancers and its relationship with prognosis.

Materials And Methods

KIF20A Expression in Human Cancers

The ONCOMINE database (www.oncomine.org) was used to examine KIF20A mRNA expression in various cancer types. P value < 0.001 and log2(fold change (FC)) > 1.5 were used as criteria. The ggplot2 package (ver. 3.6.3) in R (ver. 3.6.3, www.r-project.org) was used to visualize gene expression data from TCGA and GTEx genomic datasets, with criteria of P value = 0.01 and log2(FC) =1. Box plots were created using log2 [transcripts per million (TPM) value +1]-transformed expression data. The UALCAN website (http://ualcan.path.uab.edu/index.html) was used to evaluate cancer omics data and perform protein expression analysis of the CPTAC dataset [33]. KIF20A total protein expression levels were evaluated in primary and normal tissues. Images of IHC staining of KIF20A protein in normal and malignant tissues, including KIRC, LUAD and UCEC, were downloaded from HPA (http://www.proteinatlas.org/) and analyzed. GSCA (http://bioinfo.life.hust.edu.cn/GSCA/#/) and GEPIA2 (http://gepia2.cancer-pku.cn/#index) were used to examine the expression of KIF20A in samples of different clinical stages (stage I, stage II, stage III, and stage IV) in all TCGA tumors [34].

Prognosis Analysis

The correlation between KIF20A expression and OS or DFS across cancers was analyzed in GEPIA2. The median expression value was used to separate samples into high-expression and low-expression groups. The log-rank test was applied in the hypothesis testing.

Genetic Alteration Analysis

The KIF20A gene alteration frequency, mutation type data, mutated site information, copy number alteration (CNA) data in all cancers and the three-dimensional structure of the protein were analyzed with the cBioPortal (https://www.cbioportal.org/) tool [35].

Immune Infiltration Analysis

The ”gsva” package in R (ver. 3.6.3) was used to investigate the correlation between KIF20A expression and the levels of infiltrating immune cells, including B cells, T cells, dendritic cells, macrophages and neutrophils, based on TCGA data. In addition, the TIDE, EPIC and MCPCOUNTER algorithms in the TIMER2 (http://timer.cistrome.org) web server were applied to estimate the levels of infiltrating CAFs.

Analysis of Genes Related to KIF20A

A protein–protein interaction (PPI) network was generaated using the STRING tool (https://string-db.org/). The main parameters were as follows: minimum required interaction score [“low confidence (0.150)”], meaning of network edges (“evidence”), max number of interactors to show (“no more than 50 interactors” in the 1st shell), and active interaction sources (“experiments”). Subsequently, we used GEPIA2 to obtain the top 150 KIF20A-correlated genes in the TCGA datasets and carried out a pairwise Pearson correlation analysis of KIF20A expression and the expression of selected genes. The P values and correlation coefficients (R) were determined. Moreover, we generated a heatmap of the expression of the selected genes via the “Gene_Corr” module of TIMER2. The partial correlation (cor) values and P values were also calculated with purity-adjusted Spearman’s rank correlation test.

Results

KIF20A Expression Level Across Cancers

First, the Oncomine database was used to examine the levels of KIF20A mRNA across a wide variety of cancers. Compared to the expression in the corresponding control groups, the expression of KIF20A in cancers, including bladder, brain and central nervous system (CNS), cervical, colorectal, esophageal, gastric, head and neck, kidney, liver, lung, lymphoma, ovarian, and pancreatic cancers and sarcoma, was higher. Furthermore, two leukemia datasets and one breast cancer dataset revealed lower expression of KIF20A in cancer (Fig. 1A).

Then, we used R (v.3.6.3) to investigate RNA sequencing data from The Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx) datasets to further assess KIF20A expression across cancers. As shown in Figure 1B, the KIF20A expression in tumor tissues was significantly higher than that in the corresponding normal tissues in adrenocortical carcinoma (ACC), bladder urothelial carcinoma (BLCA), breast invasive carcinoma (BRCA), cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), cholangiocarcinoma (CHOL), colon adenocarcinoma (COAD), diffuse large B-cell lymphoma (DLBCL), esophageal carcinoma (ESCA), glioblastoma multiforme (GBM), head and neck squamous cell carcinoma (HNSC), kidney chromophobe (KICH), kidney renal clear cell carcinoma (KIRC), kidney renal papillary cell carcinoma (KIRP), brain lower grade glioma (LGG), liver hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), ovarian serous cystadenocarcinoma (OV), pancreatic adenocarcinoma (PAAD), prostate adenocarcinoma (PRAD), rectum adenocarcinoma (READ), skin cutaneous melanoma (SKCM), stomach adenocarcinoma (STAD), testicular germ cell tumors (TGCT), thyroid carcinoma (THCA), thymoma (THYM), uterine corpus endometrial carcinoma (UCEC), uterine carcinosarcoma (UCS) (all $P<0.001$) and pheochromocytoma and

paraganglioma (PCPG) (P<0.01). However, KIF20A expression was significantly lower in acute myeloid leukemia (LAML) tissue (P<0.001) than in control tissue.

Furthermore, the Clinical Proteomic Tumor Analysis Consortium (CPTAC) dataset revealed that KIF20A protein expression was higher in primary tissues than in normal controls in clear cell renal cell carcinoma (RCC), LUAD and UCEC (Fig. 1C, P<0.001). Analysis of Human Protein Atlas (HPA) data also showed that the expression of KIF20A was higher in clear cell RCC, LUAD, and UCEC than in the respective normal tissues. Representative images are presented in Figure 1D.

In addition, we used the Gene Set Cancer Analysis (GSCA) (Fig. 1E) and GEPIA2 (Fig. 1F) websites to assess the relationship between KIF20A expression and pathological stage in cancers, including ACC, BRCA, CESC, ESCA, KICH, KIRC, KIRP, LIHC and LUAD (all P<0.05), but we did not assess this relationship in the other cancers mentioned above (data not shown).

Prognostic Value of KIF20A Expression in Cancers

We divided the cancer samples into two groups based on KIF20A expression: a high-expression-group and a low-expression-group. The prognostic value of KIF20A expression across cancers was investigated with the GEPIA website. As shown in Figure 2A-J, K and L, KIF20A overexpression was associated with poor overall survival (OS) in the ACC (P=1.1e-05), KIRC (4.9e-05), KIRP (9.3e-05), LGG (P=1e-09), LICH (P=0.0034), LUAD (P=0.00046), MESO (6.3e-07), PAAD (P=0.00019), SARC (P=0.022), USC (P=0.02) and UVM (P=0.011) TCGA datasets. However, low expression of the KIF20A gene was linked to poor OS prognosis for THYM (P=0.0072). Disease-free survival (DFS) analysis (Figure 2M-X) revealed that KIF20A expression was significantly correlated with DFS in twelve cancer types: ACC (P=0.004), BLCA (P=0.012), KIRC (P=7.5e-05), KIRP (P=2.6e-05), LGG (P=6.9e-05), LIHC (P=0.00065), LUAD (P=0.023), MESO (P=0.029), PAAD (P=0.0037), PRAD (P=0.001), SARC (P=0.0014) and UVM (P=0.012). According to these findings, KIF20A expression is correlated with the prognosis of patients with various tumors.

Genetic Alterations of KIF20A Across Cancers

Human malignancies arise as a result of a build-up of genetic mutations. As such, we wanted to examine the genetic alterations of KIF20A in human tumor tissues. Renal clear cell carcinoma showed the highest incidence of KIF20A amplification, with a frequency of 5%. Endometrial carcinoma had the highest rate of KIF20A alteration (>3%), with mutation being the most common alteration type (Fig. 3A). It is worth mentioning that all cases of ocular melanoma with genetic changes had KIF20A deletion (Figure 3A). The types, locations, and case numbers of the KIF20A genetic alterations are further detailed in Figure 3B. We discovered that KIF20A missense mutations were the most common form of genetic alteration, and R445H/C mutations were observed in one case of READ and two cases of UCEC (Fig. 3b). The location of the R445H/C mutation within the KIF20A protein 3D structure is shown in Figure 3C.

Immune Cell Infiltration Analysis

As important components of the tumor microenvironment (TME), tumor-infiltrating immune cells have been found to be related to cancer formation, development, and metastasis. We initially analyzed the relationships of KIF20A expression with the levels of several types of infiltrating immune cells, including B cells, T cells (including T helper 1 (Th1) cells, Th2 cells, CD8+ T cells and regulatory T (Treg) cells), endothelial cells, macrophages and neutrophils. KIF20A expression was linked with the levels of these infiltrating immune cells to varying degrees, as shown in Figure 4. Cancer-associated fibroblasts (CAFs) have been found to influence the function of different tumor-infiltrating immune cells in the stroma of the TME. Herein, we examined the potential relationship between the level of infiltrating CAFs and KIF20A gene expression in different TCGA cancer datasets using the TIMER2, MCP-COUNTER, and EPIC algorithms. We discovered a statistically significant positive association between KIF20A expression and the predicted level of infiltrating CAFs in ESCA, human papilloma virus-negative (HPV-) HNSC, KIRC, KIRP, LGG, LIHC, MESO, PCPG, THCA, UCS, and UVM and a significant negative correlation of KIF20A expression with the predicted levels of infiltrating CAFs in TGCT (Fig. 5A). Figure 5B shows a scatterplot of the data for the above tumors produced using one algorithm. For example, according to the TIDE algorithm, KIF20A expression was positively correlated with the level of infiltrating CAFs in ESCA (Rho=0.27, P=1.64e-04).

Analysis of KIF20A-related Genes

To further elucidate the molecular mechanisms by which the KIF20A gene participates in tumorigenesis, we identified genes associated with KIF20A expression and KIF20A-binding proteins and performed pathway enrichment analyses. Based on the findings, we obtained a total of 100 KIF20A-binding proteins using the STRING tool. The interaction network of the above proteins is shown in Figure 6A. Then, the TCGA pan-cancer KIF20A expression data were analyzed by the GEPIA2 tool. As seen in Figure 6B, KIF20A expression was positively correlated with that of the KIF2C (R=0.81), CDC25 (R=0.81), KIF23 (R=0.8), CCNB1 (R=0.8) and DLGAP5 (R=0.79) genes (all P <0.001). In the majority of the described cancer types, heatmap analysis revealed a positive correlation between KIF20A expression and the expression of the five genes with the highest correlation values (Fig. 6C).

Discussion

KIF20A is a member of the kinesin-6 superfamily and can be detected both in some normal tissues (for example, liver, thymus and testis) and different kinds of tumors [36]. As a microtubule-associated motor protein localized to the Golgi apparatus, KIF20A is necessary for cell cycle mitosis and plays a role in promoting cell proliferation [37]. Previous studies have shown that KIF20A accelerates the movement of organelles by combining with the GTP-bound form of Rab6 [38]. In addition, KIF20A has been linked to clinical disorders, especially cancers [39], according to a growing number of studies. However, it is unclear whether KIF20A participates in the development of cancers via common molecular processes. Accordingly, we analyzed KIF20A gene expression in 33 distinct cancers using data from the TCGA, GTEx, and CPTAC databases, as well as additional parameters, such as gene expression, genetic alterations and immune cell infiltration.

Compared with normal tissues, different tumor tissues showed differences in KIF20A expression. Our study found that KIF20A mRNA was highly expressed in most tumors, such as ACC, BRCA and LUAD (Fig. 1). The protein expression of KIF20A in KIRC, LUAD and UCEC was also upregulated compared with that in the corresponding normal tissues. Nakamura et al. reported KIF20A protein expression in several kinds of BRCA, especially triple-negative and human epidermal growth factor receptor 2-positive BRCA [19]. Further research showed that mitotic cell death induced by paprotrain, a selective inhibitor of KIF20A, could inhibit breast cancer cell growth. Zhao et al. performed immunohistochemistry and revealed widespread overexpression of KIF20A in LUAD tissues when compared to normal lung tissues [6]. Knocking down KIF20A using small interfering RNA (siRNA) transfection technology causes cell cycle arrest in the G1 phase in lung cancer cells. The above studies have shown that KIF20A promotes tumor growth by accelerating cell proliferation. It has also been reported that overexpression of KIF20A can promote invasion capacity in glioma [16] and bladder cancer [27]. In addition, the metastatic ability of tumors was weaker when KIF20A expression was knocked down 40. Moreover, elevated KIF20A expression was significantly associated with higher tumor grade and more advanced stage [1]. The present study also showed that the levels of KIF20A gene expression were linked to pathological stage (Fig. 1). A previous study illustrated that the patients with high KIF20A expression usually had shorter OS and DFS [41]. As indicated by our study, KIF20A overexpression was linked to poor prognosis (OS) for ACC, KIRC, LGG, and other cancers (Fig. 2). In addition, KIF20A inhibition affects biological processes related to mitosis-independent angiogenesis, a crucial step in the progression of cancer [24]. In conclusion, KIF20A participates in oncogenesis through different mechanisms in different tissues.

The TME is a complicated and dynamic molecular compartment comprising cancer cells, stromal cells, cytokines, soluble growth factors and the extracellular matrix (ECM) [42]. The TME exerts a crucial role in tumor initiation and growth and eventually in the malignant transformation of normal tissue. Understanding the infiltration of immune cells, an important component in the TME, will most likely aid in unraveling the mechanisms of the development of tumors. We discovered substantial correlations between KIF20A expression in tumors and immune cell infiltration (Fig. 4). For example, in both LUSC and LUAD, tumors with high KIF20A gene expression also had a higher level of infiltrating Th2 cells. The level of infiltrating Th1 cells in LUSC samples with high KIF20A gene expression was lower than that in LUSC samples with low KIF20A expression, but there was no significant difference in the level of infiltrating Th1 cells in LUAD. Advances in science and technology have enabled the development of techniques, such as single-cell sequencing technology and spatial transcriptomics analyses, that will provide helpful information to further reveal the relationship between tumor cells and infiltrating immune cell subsets [43, 44]. CAFs are a significant cell population within the stromal compartment of the TME. Previous research showed that CAFs enhance tumor growth through the degradation of ECM, epithelial to mesenchymal transition and pro-angiogenic effects [45]. Our findings showed a link between KIF20A expression and the levels of infiltrating immune cells (CAFs) in some malignancies (Fig. 5). These results suggest that in-depth research on immune cell infiltration will further clarify the mechanisms of tumor occurrence and development, which may provide help for targeted tumor therapy.

Conclusions

To the best of our knowledge, our study is the first to completely investigate KIF20A across cancers. Moreover, KIF20A has been shown to influence prognosis and to correlate with immune cell infiltration across cancers. KIF20A, as a prognostic biomarker, might serve an immunotherapy target.

Abbreviations

ACC
adrenocortical carcinoma
BLCA
bladder urothelial carcinoma
BRCA
breast invasive carcinoma
CESC
cervical squamous cell carcinoma and endocervical adenocarcinoma
CHOL
cholangiocarcinoma
COAD
colon adenocarcinoma
DLBC
diffuse large B-cell lymphoma
ESCA
esophageal carcinoma
GBM
glioblastoma multiforme
HNSC
head and neck squamous cell carcinoma
KICH
kidney chromophobe
KIRC
kidney renal clear cell carcinoma
KIRP
kidney renal papillary cell carcinoma
AML
acute myeloid leukemia
LGG
brain lower grade glioma
LIHC
liver hepatocellular carcinoma

LUAD
lung adenocarcinoma
LUSC
lung squamous cell carcinoma
MESO
mesothelioma
OV
ovarian serous cystadenocarcinoma:PAAD:pancreatic adenocarcinoma
PRAD
prostate adenocarcinoma
READ
rectum adenocarcinoma
SKCM
skin cutaneous melanoma
STAD
stomach adenocarcinoma
TGCT
testicular germ cell tumors
THCA
thyroid carcinoma
THYM
thymoma
UCEC
uterine corpus endometrial carcinoma
UCS
uterine carcinosarcoma
PCPG
pheochromocytoma and paraganglioma

Declarations

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None.

Authors' contributions

XJ L: data analysis, validation, and manuscript writing. YQ D: data analysis. J Z: manuscript editing. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets analyzed in this study are available from the corresponding author on request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

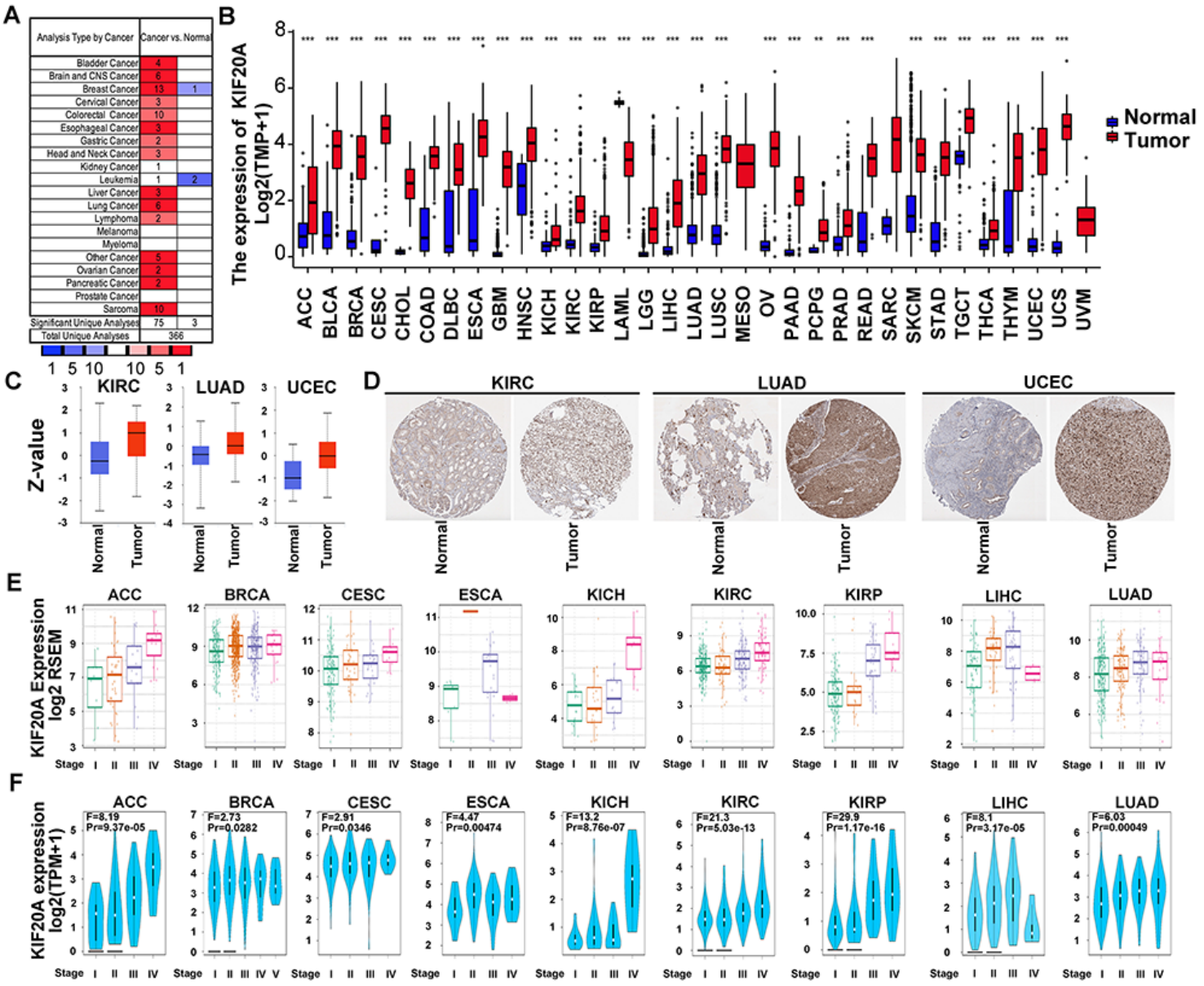

Figure 1

KIF20A expression levels in various cancers and in samples of various pathologic stages. (A) Increased and decreased expression of KIF20A was found in various cancer tissues compared to normal tissues via ONCOMINE analysis. The number in each cell represents the number of datasets. (B) The expression of the KIF20A gene in various malignancies or cancer subtypes was examined using R's ggplot2 package. ** P<0.01; *** P<0.001. (C) The KIF20A total protein level in normal and primary tissues of KIRC, UCEC, and LUAD was analyzed using the CPTAC dataset. ** P<0.01; *** P<0.001. (D) Representative immunohistochemistry images of KIF20A expression in tumor tissues and normal controls. Using the appropriate module of GEPIA (E) or GSCA (F), KIF20A gene expression by pathogenic stage (stage I, stage II, stage III, and stage IV) were examined in various cancers based on TCGA data. The expression levels are shown as log2(TPM+1) values.

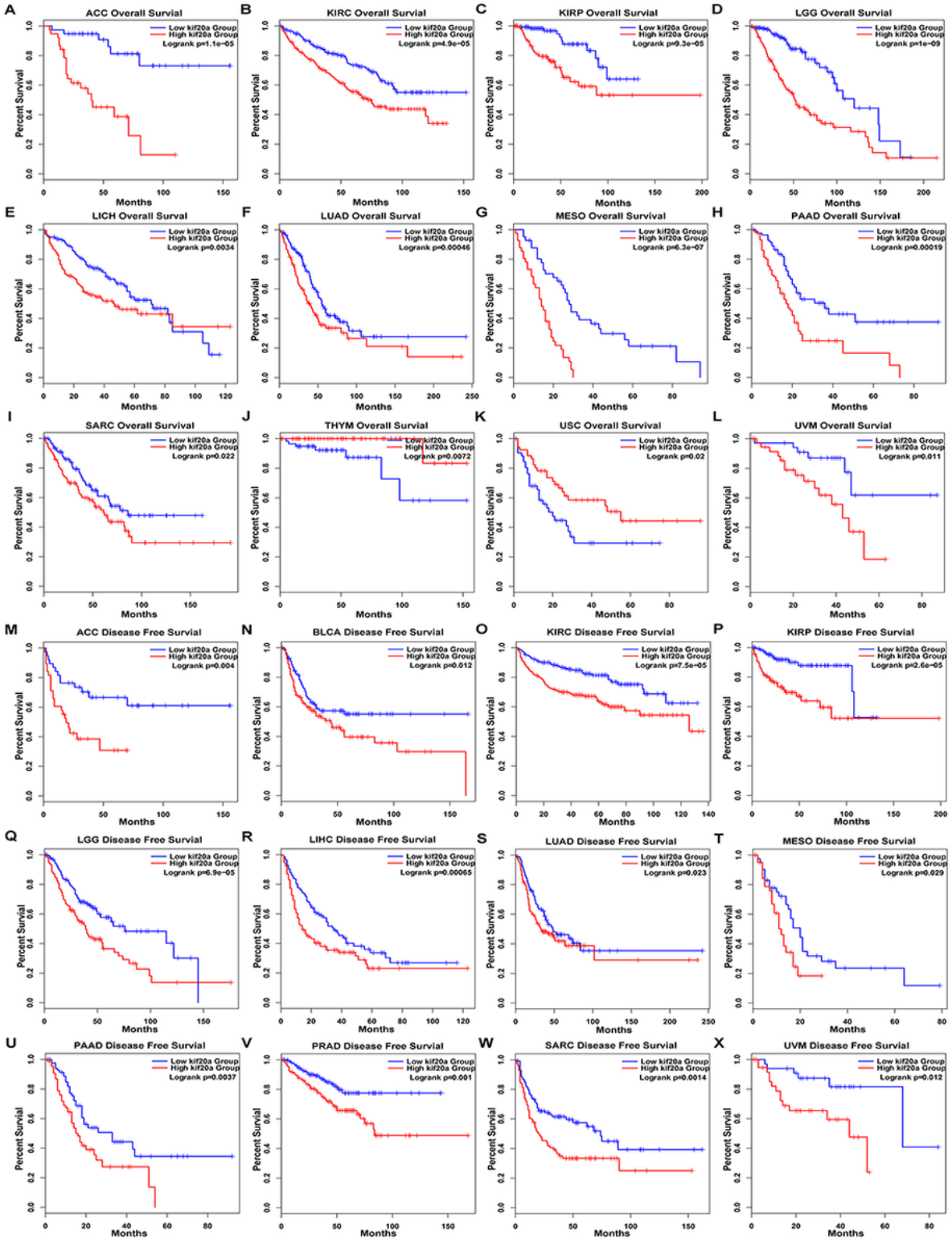

Figure 2

Correlation between KIF20A gene expression and prognosis in TCGA cancers. We used the GEPIA2 tool to analyze the relationship between KIF20A gene expression and overall survival and disease-free survival in different tumors with TCGA data. The Kaplan–Meier curves with positive results are shown.

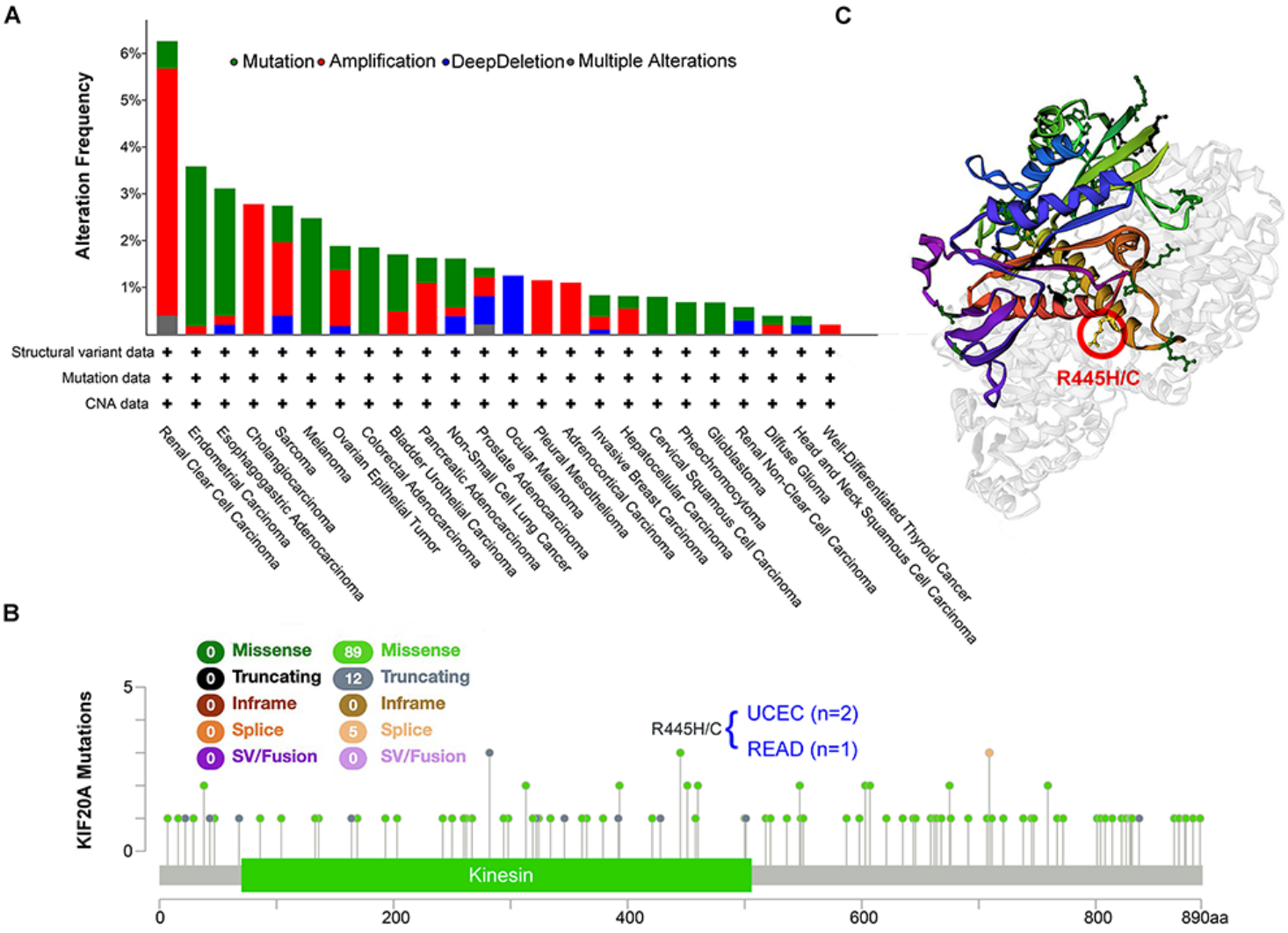

Figure 3

Mutations of KIF20A in different tumors. By using the cBioPortal tool, we examined KIF20A mutation characteristics in TCGA cancers. The frequencies of mutation types (A) and mutation sites (B) are shown. (C) In the 3D structure of KIF20A, we identified the site with the highest mutation frequency (R445H/C).

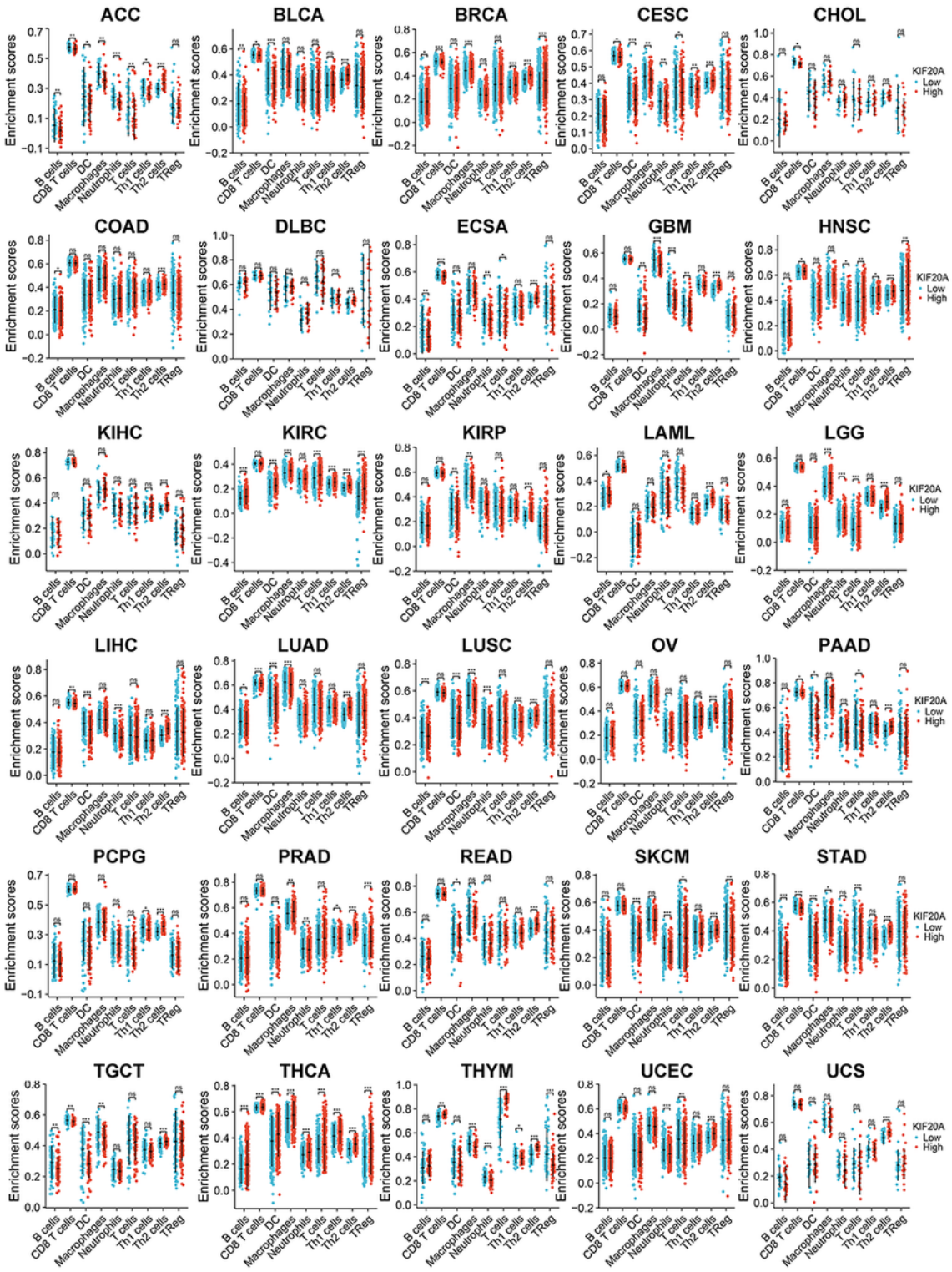

Figure 4

Correlation of KIF20A expression with the levels of infiltrating innate immune cells, T-lymphocytes and B cells in TCGA cancers. The studied innate immune cells included dendritic cells, macrophages and neutrophils. T-lymphocytes included Th1 cells, Th2 cells, CD8+ T cells and Treg cells.

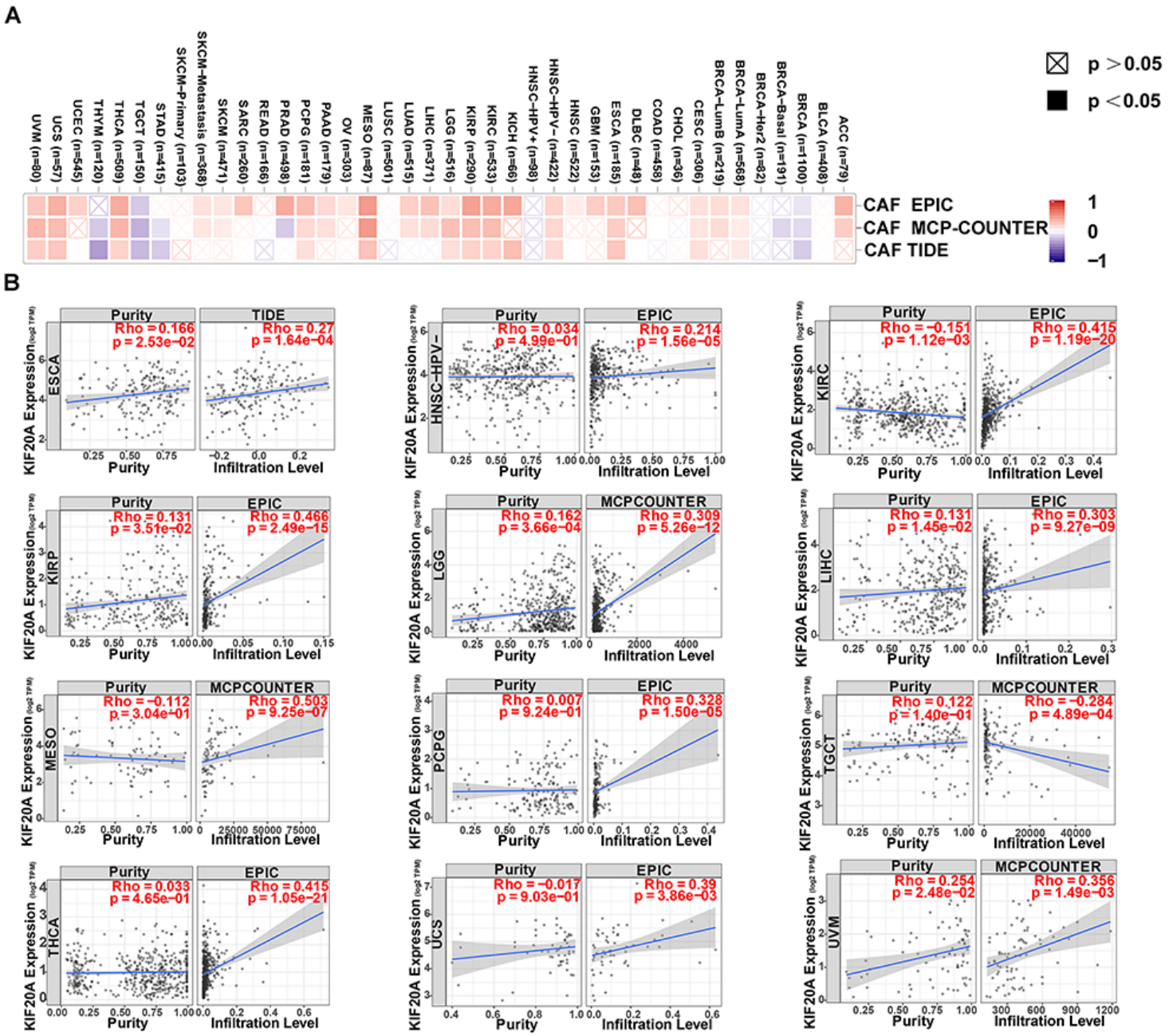

Figure 5

Analysis of the correlation between KIF20A expression and infiltration of cancer-associated fibroblasts. Different algorithms were used to explore the correlation between KIF20A gene expression and the level of infiltrating cancer-associated fibroblasts across all TCGA cancer types. The red color denotes a positive correlation (0–1), whereas the blue color denotes a negative correlation (1–0). Correlations with a P value < 0.05 were considered statistically significant. Correlation values that were statistically insignificant are denoted by a cross.

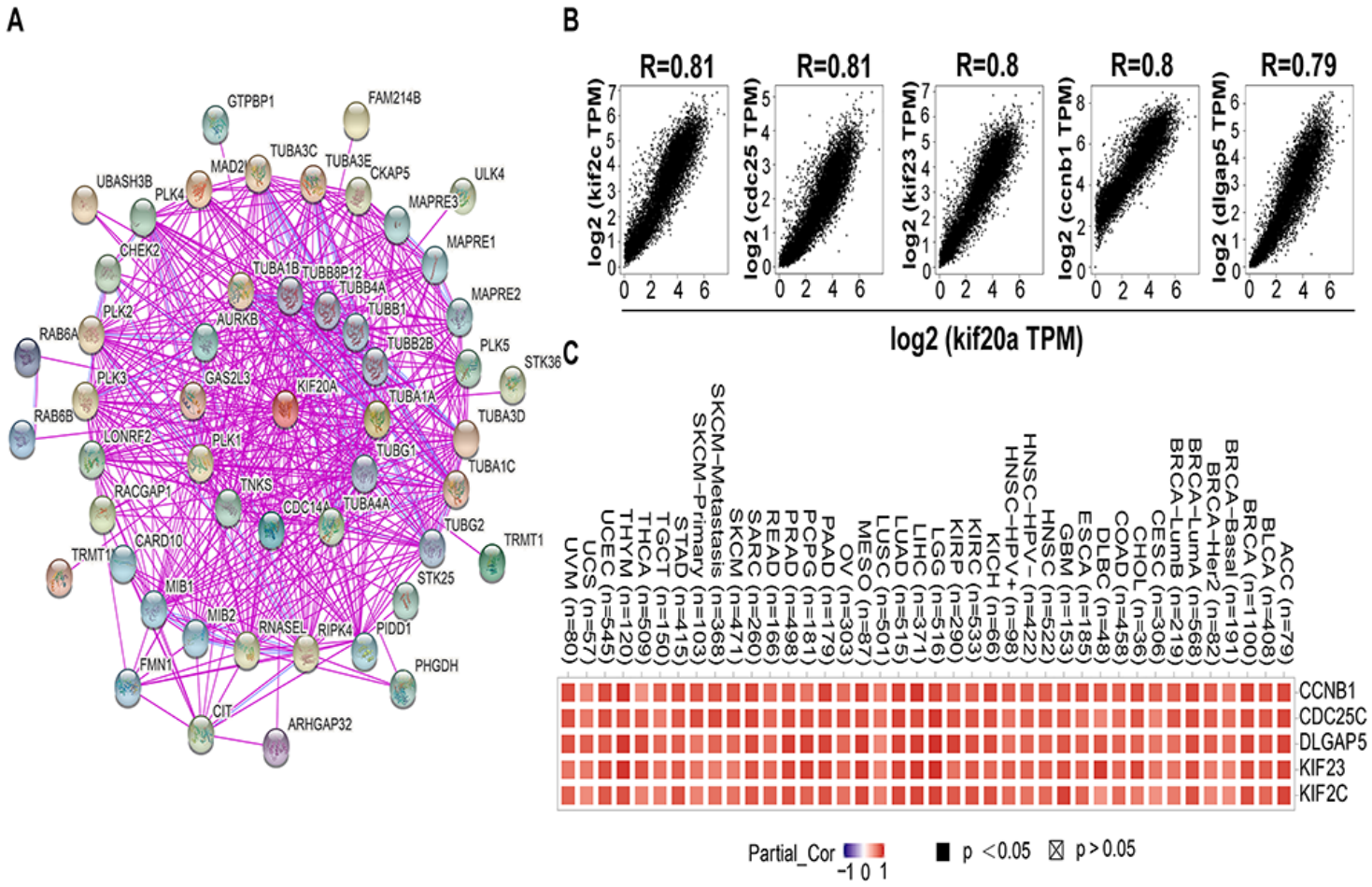

Figure 6

Enrichment analysis of genes related to KIF20A. (A) We first obtained a list of experimentally validated KIF20A-binding proteins using the STRING tool. (B) Using GEPIA2, we also obtained the top 100 KIF20A-correlated genes from TCGA projects and analyzed the correlation between KIF20A expression and the expression of the selected genes, including CDC25C, KIF2C, CCNB1, KIF23 and DLGAP5. (C) The heatmap shows the data for each cancer type.