Research Square

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A Comprehensive Analysis Revealing NEK2 as an oncogene in the Tumor Microenvironment

Lin-hong Jiang
Nanjing Medical University
Lei Li
Nanjing Medical University
Kai Yang
Xuzhou Medical University
Dan-dan Wang
Nanjing Medical University
Wen-xiu Xu
Nanjing Medical University
Su-jin Yang
Nanjing Medical University
Xiu Chen
Nanjing Medical University
Jin-hai Tang
Nanjing Medical University
He-Da Zhang (zhanghedazhd@163.com)
Nanjing Medical University https://orcid.org/0000-0001-6599-2782

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Abstract

Background

Never in Mitosis (NIMA)-related kinase 2 (Nek2), a member of the serine/threonine kinase family, localizes to centrosomes/kinetochores, which was involved in mitotic regulation. However, the clinical significance and the role of NEK2 in various cancers remained largely elusive.

Methods

ONCOMINE, Tumor Immune Estimation Resource (TIMER), Kaplan-Meier plotter database, UALCAN, GeneMANIA, String and CancerSEA Analysis were used to fully evaluate the clinical value of NEK2

Results

NEK2 was meaningfully up-regulated in the vast majority of cancers, however, the prognostic significance of NEK2 was only associated with the patients with breast cancer, lung cancer, liver cancer, renal carcinoma, pancreatic ductal adenocarcinoma, sarcoma and thyroid carcinoma. Furthermore, NEK2 expression was also correlated with individual pathological cancer stages. In addition, NEK2 participated in regulating the tumor immunity. Enrichment analysis and functional state showed NEK2 was involved in the cell cycle.

Conclusions

These findings interpret the clinic value of NEK2 in a variety of cancers, which may be a novel biomarker and therapeutic target.

Introduction

Cancer is the leading cause of death in the world, and it has been a serious threat to human health and survival [1]. According to the global cancer statistics 2020, it was reported that almost 19.3 million new cases were diagnosed as cancer, and an estimated 10 million patients died from cancer [2]. Therefore, how to find effective genes and understand their roles and mechanisms for tumors is more likely to create favorable conditions for tumor capture.

NEK2, is a member of the serine/threonine kinase family that contains eleven members (NEK1-11), which is involved in cell division and mitotic regulation [3]. NEK2 has higher sequence similarity to NIMA, which has 47% sequence identity within catalytic domains, and consists of three splice variants of NEK2A, NEK2B and NEK2C[4]. It was reported that NEK2 was over-expressed in multiple types of cancer, such as in breast cancer[5], thyroid cancer[6], colon cancer[7], hepatocellular carcinoma[8], et al. Moreover, NEK2

was involved in diverse biological function, including cell proliferation, metastatic, cell cycle, migration, drug resistance or radioresistance, and also participated in RNA splicing, DNA damage response and maintaining centrosomal structure and function[3, 4, 9]. These findings imply that NEK2 may act as an effective potential target for the treatment of cancer.

We have recognized that the tumorigenic role of NEK2 is more increasingly, but there is still a lack of knowledge of NEK2 in cancer. In this study, we focus on evaluating the expression profiles of NEK2 in a variety of tumors via online databases, and further grope for the mechanisms of NEK2 promoting tumorigogenesis. Moreover, these results suggest NEK2 may translate into critical prognostic factors and therapeutic clinical targets. Therefore, a comprehensive understanding of NEK2 role in cancers will have great clinical significance to increase the early detection rate and improve the survival rate of tumor patients.

Materials And Methods

ONCOMINE Data Analysis

ONCOMINE (https://www.oncomine.org) is a set of cancer microarray databases. NEK2 mRNA expression in various cancers is excavated through Oncomine database. Student's t test was used to perform statistical analysis. The threshold were set up as follows: $p < 0.0001$; fold change ≥ 2; gene ranking: top 10%.

UALCAN Database Analysis

UALCAN (http://ualcan.path.uab.edu/) is a clinical data from the TCGA database[10]. NEK2 expression was analyzed in cancers based on different clinical stages. $p < 0.05$ was considered to be significant.

TIMER Database Analysis

TIMER (https://cistrome.shinyapps.io/timer/) is a newly software to estimate the relationship between NEK2 and the tumor-infiltrating immune cells in cancers[11]. including CD8 + T cells, CD4 + T cells, B cells, neutrophils, dendritic cells and macrophages. $p < 0.05$ was considered to be significant.

Kaplan-Meier survival analysis

The Kaplan-Meier plotter (http://kmplot.com/analysis/) is an online website to estimate prognostic values of cancer patients[12]. In this work, the prognostic value was calculated based on median values of NEK2 expression. $p < 0.05$ was considered to be significant.

Bioinformatics analysis

String (https://string-db.org/) and GeneMANIA (http://www.genemania.org) database were utilized to build protein-protein interaction diagram. In this study, we predicted relationships between NEK2 and potential proteins.

CancerSEA Analysis

CancerSEA database (http://biocc .hrbmu .edu.cn/Cance rSEA/) was analyzed the functional role of genes in the tumor at a single-cell resolution, including proliferation, apoptosis, invasion, metastasis, cell cycle, et al. Strength > 0.3 and FDR < 0.05 was considered to be significant correlations between the gene and biological behaviour in different tumor single-cell.

Statistical Analysis

The NEK2 mRNA expression was analyzed by the Oncomine and the UALCAN database via Student's t-test. Survival curves were presented through Kaplan-Meier plot. The orrelation between NEK2 and TILs was analyzed in TIMER databases through Spearman's correlation analysis, $p < 0.05$ was considered to be significant.

Results

Aberrant Expression of NEK2 in various cancers

NEK2 mRNA expression was analyzed in various types of cancer by ONCOMINE database, and the data showed that NEK2 was significantly up-regulated in bladder cancer, brain and CNS cancer, breast cancer, cervical cancer, colorectal cancer, esophageal cancer, gastric cancer, head and neck cancer, liver cancer, lung cancer, lymphoma cancers, ovarian cancer, pancreatic cancer and stomach cancer, but down-regulated in kidney cancer and prostate cancer (Fig. 1A). Furthermore, the analysis of NEK2 expression lever using the TIMER database exhibited NEK2 was meaningfully up-regulated in the vast majority of cancers compared with the corresponding adjacent tissues, including bladder urothelial carcinoma, breast invasive carcinoma, cholangiocarcinoma, colon adenocarcinoma, esophageal carcinoma, head and neck squamous cell carcinoma, kidney chromophobe, kidney renal clear cell carcinoma, kidney renal papillary cell carcinoma, liver hepatocellular carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, prostate adenocarcinoma, rectum adenocarcinoma, stomach adenocarcinoma, thyroid carcinoma, uterine corpus endometrial carcinoma (Fig. 1B). UALCAN database showed NEK2 high expression in kidney renal clear cell carcinoma, kidney renal papillary cell carcinoma and prostate cancer (Fig. 1C). Therefore, these findings suggest that NEK2 was dyregulated in various cancers

Prognostic significance of NEK2 expression in various cancers

Soon afterwards, we analyzed the correlation between NEK2 and prognostic via Kaplan-Meier plotter database in cancers. It was exhibited that high expression of NEK2 was significantly correlated with poor prognosis in breast cancer ((OS: HR = 1.42, p = 0.00024; DFS: HR = 1.71, p = 1.8e-11; RFS: HR = 1.77, p < 1e-16 Fig. 2A–2C), lung cancer (OS: HR = 1.71, p = 1.7e-16; PPS: HR = 1.45, p = 0.0041; Fig. 2D–2E), liver cancer (OS: HR = 2.03, p = 7e-05, Fig. 2F), kidney renal clear cell carcinoma (OS: HR = 1.73, p = 0.00039 Fig. 2G), kidney renal papillary cell carcinoma (OS: HR = 3.82, p = 3.5e-05, Fig. 2H), pancreatic ductal

adenocarcinoma (OS: HR = 1.9, p = 0.0022, Fig. 2I), sarcoma (OS: HR = 1.49, p = 0.049, Fig. 2J), thyroid carcinoma (OS: HR = 3.49, p = 0.021, Fig. 2K). However, low expression of CCL14 was associated with poor OS (HR = 0.79, p = 0.0055), PPS (HR = 0.55, p = 2e-07) and FP (HR = 0.78, p = 0.018) (Fig. 2L-N), which was contrary to its expression in gastric cancer. These data demonstrated the prognostic significance of NEK2 in breast cancer, lung cancer, liver cancer, renal carcinoma, pancreatic ductal adenocarcinoma, sarcoma, thyroid carcinoma.

Analysis of NEK2 expression in individual cancer stages

We next explored NEK2 expression in individual pathological cancer stages. It was found that NEK2 was up-regulated in breast cancer, lung adenocarcinoma, lung squamous cell carcinoma, liver cancer, kidney renal clear cell carcinoma, kidney renal papillary cell carcinoma compared with adjacent tissues (Fig. 3), this suggests that NEK2 may be involved in tumorigenesis. However, NEK2 expression was no significant correlation between pathological stages and adjacent tissues in pancreatic ductal adenocarcinoma, and thyroid carcinoma. Furthermore, NEK2 expression was lower in early-stages of breast cancer, lung adenocarcinoma, liver cancer, kidney renal papillary cell carcinoma and kidney renal clear cell carcinoma compared to late-stage (Fig. 3), representing a role of oncogenes in cancer progression and development.

Correlation between NEK2 and TILs

Subsequently, we explored the correlation between NEK2 expression and immunocytochemical markers of immune cells (purity, CD8 + T cells, CD4 + T cells, neutrophils, B cells, macrophages and dendritic cells). It was found that NEK2 was associated with purity, B cells, CD8 + T cells, CD4 + T cells, macrophages, neutrophils and dendritic cells in kidney renal clear cell carcinoma and liver hepatocellular carcinoma, and associated with B cells, CD8 + T cells, CD4 + T cells, macrophages, neutrophils and dendritic cells in thyroid carcinoma. In addition, NEK2 was positively correlated with purity, B cells, CD4 + T cells, neutrophils and dendritic cells in breast cancer, however, NEK2 was only correlated with CD4 + T cells or B cells in BRCA Basal or BRCA Her2, separately. Besides, NEK2 was negatively correlated with CD4 + T cells in lung adenocarcinoma, lung squamous cell carcinoma, pancreatic adenocarcinoma, sarcoma, but positively associated with CD4 + T cells in breast cancer, kidney renal clear cell carcinoma, liver hepatocellular carcinoma and thyroid carcinoma (Fig. 4).

Enrichment Analysis and Functional state of NEK2 in various cancers

Afterwards, we explored the potential mechanism of NEK2 in cancers through String and GeneMANIA analysis. It was found that NEK2 was correlated with CDC family gene (CDC16, CDC20, CDC26, CDC27), MAD2L1, FZR1, et al (Highest confidence (0.9)) (Fig. 5A). Indeed, NEK2 was also correlated with CDK1, FOXM1, PLK4, DEPDC1, et al (Fig. 5B). Additionally, we further excavated NEK2 enrichment analysis through PathCards database. The results showed that NEK2 was primarily enriched for CDK-mediated phosphorylation and removal of Cdc6, cell cycle and organelle biogenesis and maintenance (Fig. 5C). Whereafter, we further explored the functional state of NEK2 at the single-cell level via CancerSEA database. It was showed that NEK2 was positively correlated with cell cycle, differentiation, DNA damage,

DNA repair, invasion and proliferation in lung adenocarcinoma (LUAD); NEK2 was positively correlated with cell cycle, DNA damage and proliferation, while negatively correlated with differentiation, inflammation and metastasis in breast cancer (BRCA); additionally, NEK2 was positively correlated with cell cycle, DNA damage, DNA repair and proliferation, while negatively correlated with angiogenesis in coloretal cancer (CRC). However, NEK2 was not significantly associated with 14 functional states in NSCLC.

Discussion

NEK2, a significant mitotic kinase, could promote mitosis though phosphorylation of the mitotic component, and acted an important role in participating in cell cycle process through promoting centrosome splitting decomposition of mitosis[13]. Furthermore, NEK2 has been identified as an oncogene associated with the development of various cancers, such as, overexpression of NEK2 promoted hepatocellular carcinoma cell proliferation, migration, invasion and drug resistance via activating Akt and Wnt signaling pathways [9]. Knockdown of NEK2 inhibited cell growth and migration through mediating β-catenin/Myc/KDM5B/H3K4me3 pathway in gastric cancer. Down-regulation of NEK2 suppressed breast cancer cell proliferation, clone formation, invasion, and increased cell apoptosis via ERK/MAPK pathway[14]. Indeed, deregulation of NEK2 also associated with prognosis of various types of cancer. Prostate cancer patients with high expression of NEK2 were significantly associated with poor recurrence free survival [15]. The overall survival and disease-free survival of hepatocellular carcinoma patients with high expression of NEK2 was shorter than those patients with low expression of NEK2[16]. Therefore, NEK2 may be a novel and promising biomarker.

In this work, ONCOMINE database showed NEK2 had higher expression in most cancer tissues compared with the corresponding adjacent tissues, except kidney cancer and prostate cancer. Indeed, NEK2 was significantly up-regulated in bladder urothelial carcinoma, breast cancer, cholangiocarcinoma, colorectal cancer, esophageal carcinoma, head and neck squamous cell carcinoma, kidney cancer, liver cancer, lung cancer, prostate adenocarcinoma, stomach adenocarcinoma, thyroid carcinoma, uterine corpus endometrial carcinoma by TIMER database analysis. However, this results showed the opposite trend of NEK expression in kidney cancer and prostate adenocarcinoma, then we further look for other databases to confirm NEK2 expression. It was exhibited NEK2 was up-regulated in kidney renal clear cell carcinoma, kidney renal papillary cell carcinoma and prostate cancer by UALCAN analysis. Therefore, these findings suggest that NEK2 could almost act as an oncogene in cancers. Moreover, Kaplan-Meier Plotter survival analysis demonstrated that high expression of NEK2 was significantly correlated with worse prognosis in breast cancer, lung cancer, liver cancer, renal carcinoma, pancreatic ductal adenocarcinoma, sarcoma and thyroid carcinoma. Besides, NEK2 expression was also involved in pathological cancer stages, and NEK2 expression in patients with early-stages cancers was lower than late-stage cancers, such as, breast cancer, lung adenocarcinoma, liver cancer, kidney renal papillary cell carcinoma and kidney renal clear cell carcinoma. Therefore, NEK2 was not only an important indicator of assessing tumor prognosis, but also a pivotal basis for determining staging.

Tumor microenvironment has been acted an important role in tumor immunology, and regarded as potential prognostic biomarker in numerous cancers, among them, infiltrating immune cells account for a large proportion[17]. CCL14 was significantly associated with immune infiltration in 39 types of cancer, moreover, low expression of CCL14 was associated with higher infiltration of the majority of immune cell and worse prognosis in hepatocellular carcinoma [18]. In our study, it showed that NEK2 was associated with purity, B cells, CD8 + T cells, CD4 + T cells, macrophages, neutrophils and dendritic cells in 2 cancer types with a valuable prognosis. Additionally, NEK2 expression was significant correlated with tumor purity in 7 cancer types, B cells in 6 cancer types, CD4 + T cells in 8 cancer types, CD8 + T cells in 4 cancer types, macrophages in 6 cancer types, neutrophils in 5 cancer types, and dendritic cells in 4 cancer types. Besides, the regulation trend of NEK2 on immune infiltration cell varies with different tumors. Therefore, NEK2 has a potential role in regulating tumor immunology and it can act as a tumor prognosis biomarker.

Although we studied and integrated information from different databases on NEK2, and proved that NEK2 could act as an oncogene to regulate the initiation and progression of cancers. Currently, research on NEK2 was still in the basic stage, so there were still great restrictions and insufficient research on NEK2. It demonstrated that NEK2 was correlated with CDC family gene, FZR1, CDK1, FOXM1, PLK4, DEPDC1, et al. CDC20 was also an oncogene that accelerated promotes anaphase and mitotic progression, promoting cell proliferation[19]. CDC27 was one of the pivotal components of the anaphase promoting complex, which could control mitosis and chromosomal separation via regulating APC/C (Anaphase Promoting Complex or Cyclosome) activity in cyclin degradation, and then regulated the cell cycle transition in cell division[20]. FZR1, a co-activator of the APC/C, was sensitized by dephosphorylation of inactivated CDK1 in anaphase of mitosis, thus mediating cell cycle and apoptosis [21]. PLK4 has been confirmed to mediate centriole duplication through interacting with various central somatic proteins in the cell cycle[22]. These genes were correlated with cell cycle or cell proliferation. Indeed, NEK2 was primarily enriched for CDK-mediated phosphorylation and removal of Cdc6, or cell cycle by path enrichment analysis, therefore, NEK2 could mediate cell biological function by regulating related genes or pathways. In addition, NEK2 was all correlated with cell cycle, DNA damage and proliferation in LUAD, BRCA and CRC, and was associated with invasion or metastasis in LUAD or BRCA through single-cell level analysis. Overall, NEK2 acted as an important role in cell cycle and proliferation in various cancers, which needs to be confirmed by subsequent experiments.

Conclusion

In summary, we comprehensively illuminated NEK2 expression profiles and prognostic value in various types of cancer, and NEK2 expression has significant prognostic value in breast cancer, lung cancer, liver cancer, renal carcinoma, pancreatic ductal adenocarcinoma, sarcoma, thyroid carcinoma. Therefore, NEK2 will be a novel prognostic evaluation indicator and strategy for clinical treatment of cancer.

List Of Abbreviations

Nek2 Never in Mitosis (NIMA)-related kinase 2

NSCLC Non-small-cell carcinoma

CRC coloretal cancer

LUAD lung adenocarcinoma

Declarations

Competing interests: The authors declare that they have no conflict of interest.

Ethics approval and consent to participate This article does not contain any studies with human participants performed by any of the authors.

Consent for publication The authors confirm that the paper has not been published elsewhere

Availability of data and material The authors affirm that all data necessary for confirming the conclusions of the article are present within the article, figures, and tables.

Authors Contribution: the authors declare that all data were generated in-house and that no paper mill was used.

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Figures

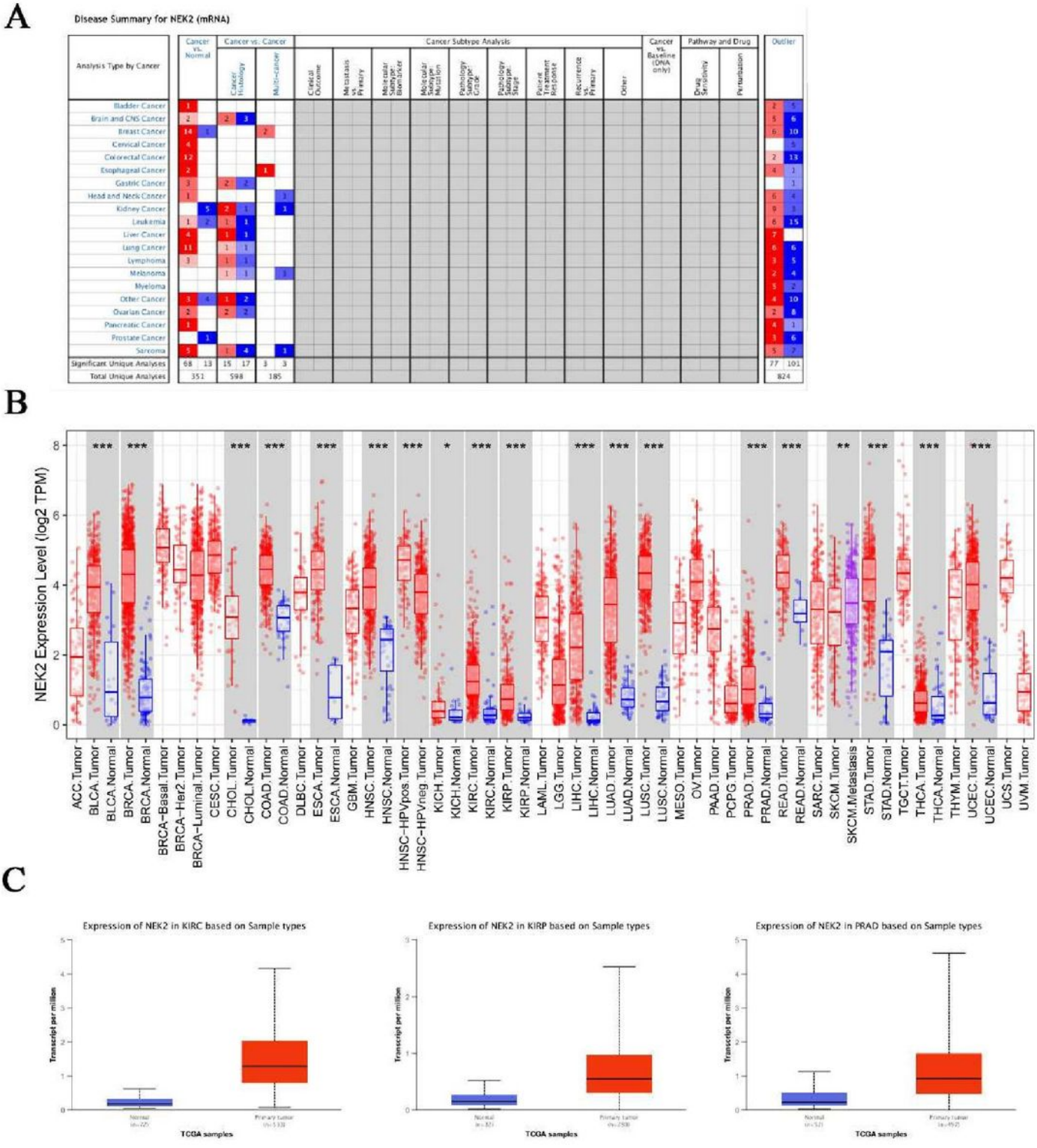

Figure 1

Aberrant Expression of NEK2 in various cancers A. The transcription level of NEK2 was analyzed in various types of cancer by ONCOMINE database (red represents over-expression, or blue represents down-expression). **B.** NEK2 expression was analyzed in various types of cancer by TIMER database. **C.** Boxplot demonstrated NEK2 expression in kidney renal clear cell carcinoma, kidney renal papillary cell carcinoma and prostate cancer.

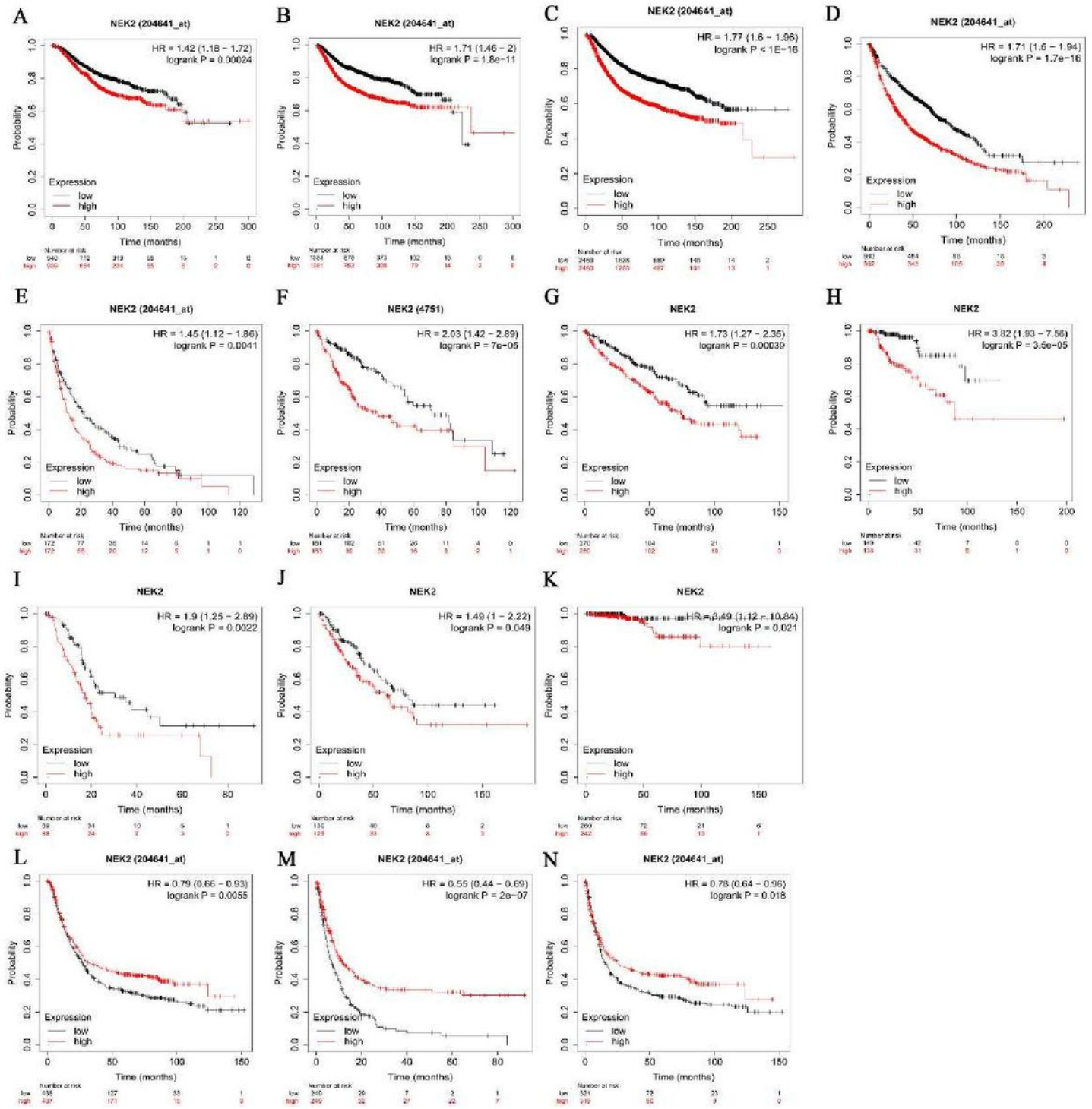

Figure 2

Prognostic significance of NEK2 expression in various cancers. A-N. Kaplan-Meier survival analysis was used to perform prognosis for patients with high (red) and low (black) NEK2 expression in various cancers.

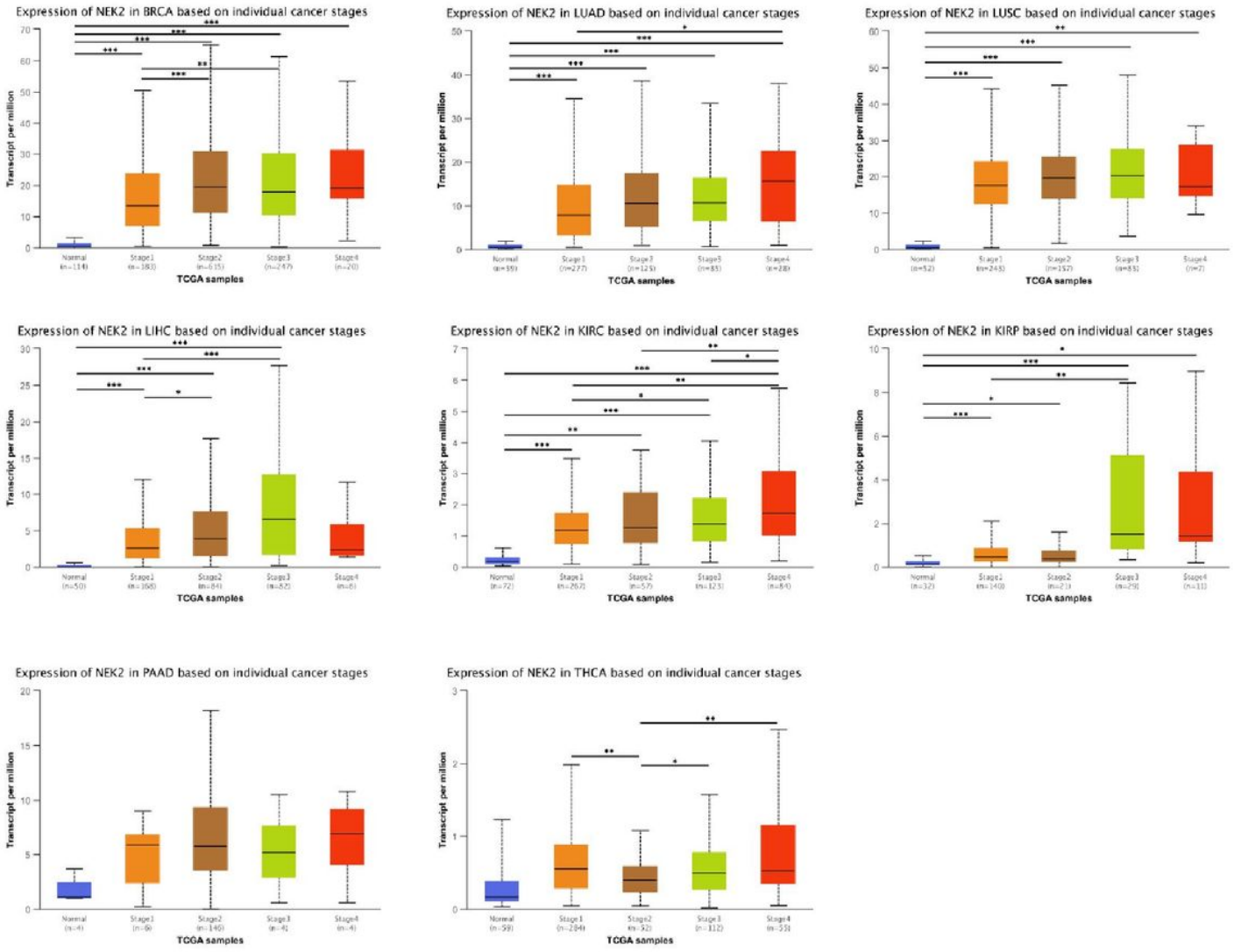

Figure 3

Analysis of NEK2 expression in individual cancer stages. A. Boxplot demonstrated NEK2 expression in normal individuals and cancer patients with different clinical stages. *p<0.05; **p<0.01; ***p<0.001.

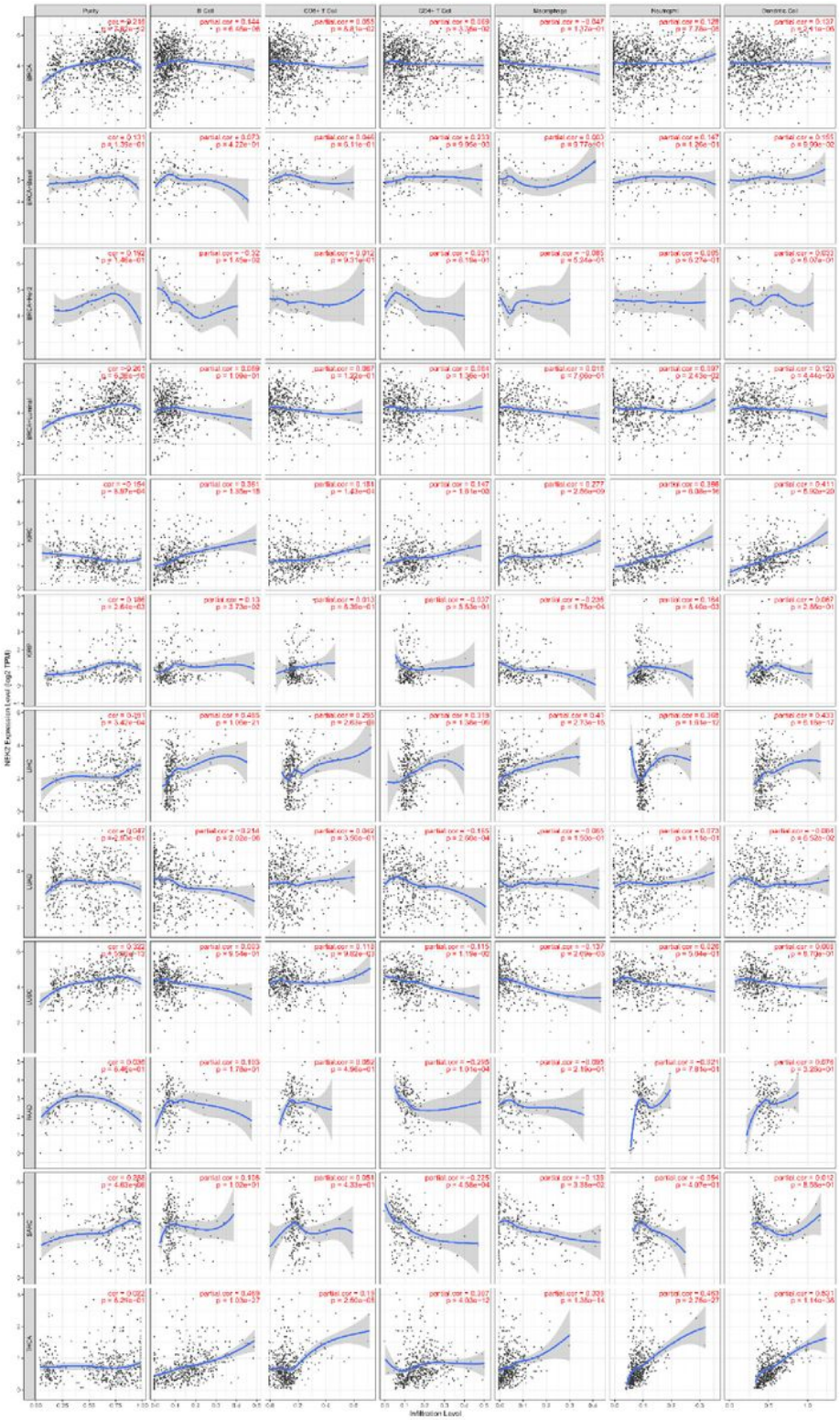

Figure 4

Correlation between NEK2 and TILs. NEK2expression was closely associated with immune infiltration levels in various cancers.

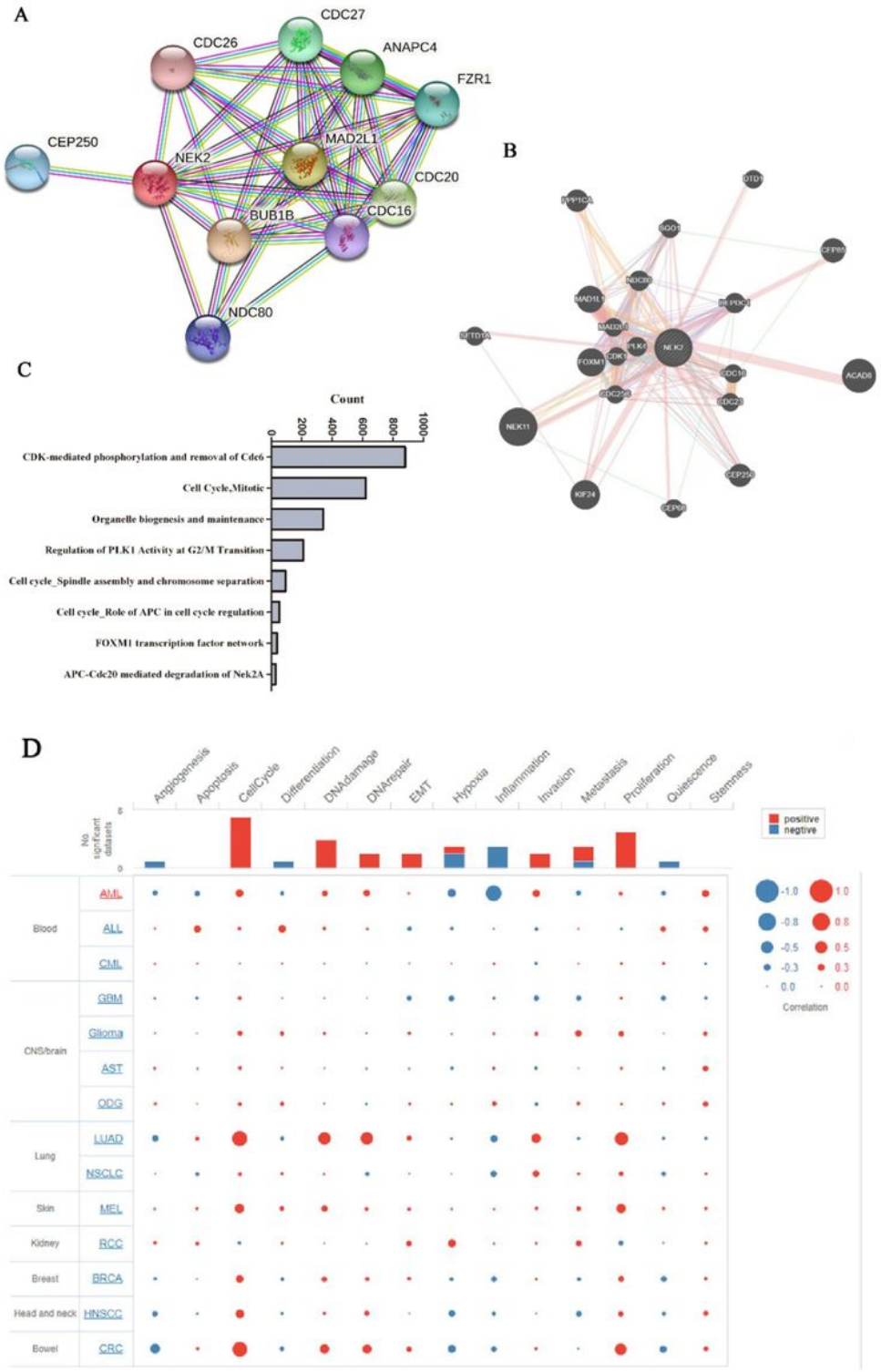

Figure 5

Enrichment Analysis and functional state of NEK2 in various cancers. A, B. Protein–protein interaction network of NEK2 by String and GeneMANIA database. **C.** PathCards enrichment term analyses for NEK2. **D.** The functional state of NEK2 in cancers at the single-cell level.