

Expression Level and Prognostic Potential of MAP3K8 in Human Cancers Based on Data Mining

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Primary research

Keywords: MAPK kinase kinase 8 (MAP3K8), expression, methylation, prognosis, protein-protein interaction (PPI), functional enrichment analysis

Posted Date: March 9th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-276370/v1>

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Abstract

Background: MAPK kinase kinase 8 (MAP3K8) is a member of the MAP3K family with a major role in the regulation of the MAPK pathway and immune response. Differential expression of MAP3K8 is closely correlated with tumorigenesis. In this study, we used bioinformatics tools to explore expression level, prognostic values, and interactive networks of MAP3K8 in human cancers.

Methods: Expression profile of MAP3K8 was analyzed using the OncoPrint Platform, the Gene Expression Profiling Interactive Analysis (GEPIA), and UALCAN. Survival analysis was evaluated via UALCAN, GEPIA, and DriverDBv3 databases. Then, MAP3K8 related functional networks were explored within GeneMANIA and Cytoscape. Moreover, Metascape was used to analyze Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways.

Results: We found that MAP3K8 was down-expressed in most cancer samples compared with paired normal tissues. Results from databases revealed that high MAP3K8 expression was associated with poorer prognosis of OS in kidney renal clear cell carcinoma (KIRC) (GEPIA: Log-rank $p=0.006$, HR=1.5; DriverDBv3: Log-rank $p=1.68e-07$, HR=2.21; UALCAN: $p=0.002$) and thymoma (THYM) (DriverDBv3: Log-rank $p=0.011$, HR=5.44; UALCAN: $p=0.041$). High MAP3K8 expression was correlated with better prognosis of OS in mesothelioma (MESO) (GEPIA: Log-rank $p=0.016$, HR=0.56; DriverDBv3: Log-rank $p=0.002$, HR=0.46) and skin cutaneous melanoma (SKCM) (GEPIA: Log-rank $p=0.00092$, HR=0.64; UALCAN: $p=0.017$). Gene regulation network suggested that MAP3K8 was mainly involved in immune cell function and MAPK signaling pathway.

Conclusions: MAP3K8 overexpression was correlated with improved survival in MESO and SKCM, and with damaged survival in KIRC and THYM, reemphasizing the potential for identifying predictive biomarkers and therapeutic targets focused on MAP3K8 and the MAPK pathway.

Background

Cancer is one of the most fatal killers of the man, which claimed approximately 607,000 deaths in the United States annually [1]. The long-term trends in cancer incidence is volatile largely due to the rapid changes in disease detection methods and modifiable risk factors [2]. Cancer death rates has continuously declined since 1990s, resulting in millions of fewer cancer deaths, although the socioeconomic status, ethnicity, and geographic factors influence the cancer death rates [1]. The fights against cancer to improve survival includes but it is not limited to steady reductions in risk factors, advances in early-stage detection and therapeutic strategies, and deeper researches in cancer biology [1, 2]. However, cancer does not simply grow to race with the development of anti-cancer therapeutics, such as surgery, chemotherapy, radiotherapy, but rather energetically resorts to various tactics to delay, alter, or even stop them [3]. Backed up by new approaches such as target therapy and immunotherapy, these treatment options inevitably lead to a failure in the control of tumor growth, manifesting as recurrence, metastasis, drug resistance. These mechanisms develop continuously during the progression of cancer

and demonstrate reductions in cancer-related overall survival. However, these clinical problems are still not well solved, and the translation of new discoveries from fundamental researches to the clinical benefits remains challenging. In addition to enhancing the efficacy of treatments and exploiting new strategies, finding sensitive prognostic indicators is also a favorable progress against cancer. Therefore, it is urgent to explore more potential biomarkers of diagnosis and prognosis.

The mitogen-activated protein kinase (MAPK) cascades are mainly composed of 5 kinase families including MAPK kinase kinase (MAP4K), MAPK kinase (MAP3K), MAPK kinase (MAP2K), MAPK, and MAPK-activated protein kinases (MAPKAPK), which are critically involved in the pathogenesis of malignant tumors and inflammatory diseases [4, 5]. MAP3K8 (also called TPL2, Cot) is a MAP3K with a major role in the activation of the MAPK pathways. The encoded proteins of MAP3K8 contain a serine/threonine kinase domain, an amino-terminal region, and a carboxy-terminal tail which carries sequences important for regulation of catalytic activity of MAP3K8 [6]. Early studies identified the MAP3K8 gene as a proto-oncogene activated by C-terminal truncation *in vivo* [7]. In a screen for transforming genes from a human thyroid carcinoma cell line, a deletion in C-terminal was observed [8]. Nevertheless, mutations in MAP3K8 are rarely observed in human cancers [4, 5]. Whilst elevated or reduced transcriptome profiles of MAP3K8 have been reported in human cancers according to our inspection of Oncomine database (<http://www.oncomine.org>). MAP3K8 conveys various oncogenic signals in a variety of human solid tumors [4, 9, 10]. MAP3K8 gene expression is up-regulated and amplified in breast cancer specimens, which directly interacts with Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (Pin1) and induces the phosphorylation of Pin1 on Ser16 [11]. In addition, MAP3K8 kinase contributes to disease progression of clear cell renal cell carcinoma through activated MAPK signaling and cross-talk with chemokine (C-X-C motif) ligand 12 (CXCL12) [12]. Whereas some studies indicate that MAP3K8 may have a negative role in tumor growth, under certain conditions MAP3K8 may function as tumor suppressor [4, 5]. For example, MAP3K8 knockout mice showed a significantly higher incidence of tumor initiation and faster malignant progression of skin tumors in a two-stage skin carcinogenesis mode [13]. The double-sided effects of MAP3K8 originate from the specific upstream and downstream signaling environment of each tumor, since MAP3K8 interacts with various signaling components [14].

Online tumor databases have significantly developed in recent years and are constantly evolving, which can be used to compare genetic data for a better understanding of biological pathways and regulatory mechanisms associated with cancers. Moreover, the integrative analysis of tumor databases using bioinformatics methods will explore predictive indicators of clinical outcomes and potential regulatory networks involved in cancer biology. In addition, image and signal processing bioinformatics techniques make it possible to extract useful information from massive tumor databases to visualize prognostic roles of genes and proteins. Herein, using tumor databases and bioinformatics tools to explore differently expressed genes (DEGs) in cancer samples is a plausible way to identify genes related to cancer prognosis. In this study, we comprehensively analyzed MAP3K8 expression and prognostic value of cancer patients via databases such as the Oncomine, GEPIA, UALCAN, and DriverDBv3, and found that MAP3K8 expression is down-regulated in most cancers and highly correlated with overall survival (OS)

and disease-free survival (DFS). We further investigated the functional network of MAP3K8 using the GeneMANIA and Metascape. Taken together, these findings suggest that MAP3K8 can serve as an effective prognostic biomarker in cancer patients.

Materials And Methods

Analysis of MAP3K8 expression

MAP3K8 mRNA expression differences were investigated in various cancer types between tumor and normal samples within the OncoPrint Platform (<https://www.oncoprint.org/resource/login.html#>), which is the largest oncogene chip database [15]. The OncoPrint database provides solutions for researchers with robust, peer-reviewed analysis methods and a powerful set of analysis functions that compute gene expression signatures. The OncoPrint Platform has been used as a foundation for ground-breaking discoveries with unique features that include more than 700 independent and high-quality datasets consisting of approximately 87,000 cancers and normal samples. To repeatedly verify the expression level of MAP3K8 in tumor and cancer tissues, we further applied the GEPIA (<http://www.gepia.cancer-pku.cn/index.html>) [16]. GEPIA is a newly developed interactive web server for analyzing the RNA sequencing expression data of 9,736 tumors and 8,587 normal samples from the Cancer Genome Atlas (TCGA) and the Genotype-Tissue Expression (GTEx) project. The results from the OncoPrint Platform and GEPIA database are displayed with the P -value of 0.01, fold change of 2. In addition, UALCAN (<http://www.ualcan.path.uab.edu/index.html>) was used to find differential expression of MAP3K8 according to tumor grade and histology subtype and P -value < 0.05 was considered significant [17].

Identifying prognostic potential of MAP3K8

GEPIA provides customizable survival analysis based on tumor/normal differential gene expression according to cancer types or pathological stages. We used GEPIA to find correlation between MAP3K8 expression and survival, including OS and DFS, in different cancers. The HR and P or Cox P values from a log-rank test were included in the plot. Additionally, UALCAN was used to analyze survival information based on MAP3K8 expression level and evaluate promoter DNA methylation information of MAP3K8 in different cancer types. Finally, DriverDBv3 (<http://www.driverdb.tms.cmu.edu.tw>) was used to examine the prognostic potential of MAP3K8 gene expression levels in different human cancers [18]. Survival-relevant with log-rank P -value < 0.05 was considered significant.

Constructing protein-protein interaction (PPI) networks

GeneMANIA (<http://www.genemania.org>) finds other genes that are related to a set of input genes, using a very large set of functional association data [19]. This user-friendly online tool can analyze gene or gene lists by the bioinformatics methods, including protein and genetic interactions, pathways, co-expression, co-localization and protein domain similarity. We use GeneMANIA to predict the function and visualized the gene networks by imputing MAP3K8. Cytoscape (<https://www.cytoscape.org>) was also used to visualize the results of the PPI network by searching PSICQUIC (<http://www.psicquic.github.io>) in

selected databases [20]. In this study, we chose the BioGrid database (<https://www.thebiogrid.org>) to import PPI networks of MAP3K8. Cytoscape MCODE plugin-in was used to provide access to select hub modules of PPI network of MAP3K8.

Functional enrichment analysis

The interactive gene list of MAP3K8 constructed by GeneMANIA were then all input into the Metascape (<http://www.metascape.org/gp/index.html#/main/step1>) for further function and enrichment pathways [21]. We used Metascape to perform Gene Ontology (GO) analysis including biological processes (BP), cellular component (CC) and molecular function (MF), and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis of MAP3K8. P -value <0.05 was considered as statistically significant.

Results

Identification of differential expression of MAP3K8 in human cancers

We identified the differential expression of MAP3K8 between tumor and paired normal samples on the Oncomine Platform and GEPIA website. The Oncomine Platform totally included 453 unique analyses for MAP3K8, of which 15 significant unique analyses demonstrated up-regulated expression of MAP3K8 in human cancers including brain and central nerve system cancer, colorectal cancer, gastric cancer, kidney cancer, prostate cancer, and other cancer. Meanwhile, down-regulated expression of MAP3K8 was seen in bladder cancer, brain and central nerve system cancer, breast cancer, head and neck cancer, leukemia, lung cancer, lymphoma, sarcoma, and other cancer, based on 38 significant unique analyses (Figure 1A). Furthermore, the GEPIA website was applied to reveal the gene expression profile of MAP3K8 across all tumor samples and paired normal tissues. Among the cancer gene profiles obtained from TCGA and GTEx, we screened 4 kinds of cancer that displayed down-regulated expression of MAP3K8, including adrenocortical carcinoma (ACC), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), and skin cutaneous melanoma (SKCM) (Figure 1B). From the gene expression profile of MAP3K8 across all analyses, we found a lower expression level of MAP3K8 in cancer samples compared with paired normal tissues. To explore the relationship between clinicopathologic parameters and MAP3K8 expression, we analyzed MAP3K8 expression level in all cancers using subgroup factors such as tumor grade, race, gender, age, and histology. Our results indicated that MAP3K8 expression level is significantly related with tumor grade and cancer subtypes in kidney renal clear cell carcinoma (KIRC), which was marked by that patients with grade 4 KIRC and ccB subtype showed higher MAP3K8 level than those with grade 3 KIRC and ccA subtype, respectively ($P<0.05$). Compared with SKCM patients at the age of 41 to 60 years, patients at age between 21 - 40 years expressed more MAP3K8. For THCA, patients with classical thyroid papillary carcinoma, follicular thyroid papillary carcinoma, and other subtypes showed higher level of MAP3K8 than patients with tall thyroid papillary carcinoma ($P<0.05$) (Figure 2).

Promoter methylation level of MAP3K8 gene in human cancers

The UALCAN database was used to explore the level of MAP3K8 promoter methylation in human cancers. Our results suggested that the promoter methylation level of MAP3K8 in primary tumor of KIRC was higher than normal tissues ($P<0.001$). In addition, grade 1 KIRC had higher level promoter methylation of MAP3K8 than grade 2 and 3 tumor ($P<0.001$). Interestingly, metastatic tumor, but not primary tumor, of SKCM had higher level promoter methylation of MAP3K8 than compared normal tissues ($P<0.05$). Moreover, further subgroup analysis of promoter methylation showed significance based on cancer stage in THCA. Patients with stage 4 thyroid carcinoma (THCA) had higher level promoter methylation of MAP3K8 than that with stage 2 ($P<0.05$) (Figure 3).

Prognostic potential of MAP3K8 in different human cancers

To determine the prognostic value of MAP3K8 in human cancers, we performed survival analysis based on the GEPIA, DriverDBv3 and UALCAN databases. We only showed Kaplan-Meier (KM) curves that displayed significant prognostic value of MAP3K8 in cancers that have been conducted survival analysis based on at least 2 databases. KM curves of MAP3K8 in 7 kinds of cancers, including cervical squamous cell carcinoma (CESC), GBM, kidney renal papillary cell carcinoma (KIRP), brain lower grade glioma (LGG), LUAD, SARC, and uveal melanoma (UVM), were not displayed because only one database showed significant prognostic value of MAP3K8 (Figure 4). Results from GEPIA revealed that high MAP3K8 expression level was associated with poorer prognosis of OS in KIRC (Log-rank $p=0.006$, HR=1.5), and correlated with better prognosis of OS in mesothelioma (MESO) (Log-rank $p=0.016$, HR=0.56), SKCM (Log-rank $p=0.00092$, HR=0.64), and DFS in THCA (Log-rank $p=0.036$, HR=0.53) (Figure 5). The relationships obtained from DriverDBv3 between MAP3K8 expression and prognosis indicated that high MAP3K8 expression negatively affects OS in KIRC (Log-rank $p=1.68e-07$, HR=2.21) and thymoma (THYM) (Log-rank $p=0.011$, HR=5.44); high MAP3K8 expression significantly improved OS in MESO (Log-rank $p=0.002$, HR=0.46) (Figure 6). Additionally, survival analysis from UALCAN showed that high MAP3K8 expression was correlated with poorer clinical outcome in KIRC ($p=0.002$), THCA ($p=0.028$) and THYM ($p=0.041$), and with better prognosis in SKCM ($p=0.017$) (Figure 7).

Protein-protein interaction network analysis

The GeneMANIA online website and Cytoscape software were used to establish the interactions of MAP3K8. The PPI networks from the GeneMANIA website revealed a correlation among genes for MAP3K8. The gene sets enriched for MAP3K8 were responsible for toll-like receptor 3 signaling pathway, toll-like receptor 2 signaling pathway, toll-like receptor signaling pathway, pattern recognition receptor signaling pathway, innate immune response-activating signal transduction, activation of innate immune response, and protein serine/threonine kinase activity (Figure 8). In addition, the Cytoscape software was used to visualize the network of MAP3K8 by searching the BioGrid database. Each node, linked by edges, stood for an enriched term colored by the cluster-ID (Figure 9A). Meanwhile, the network of core modules of genes, including REL, RELA, TNIP2, NFKB1, NFKB2, and NFKBIA, were also constructed by MCODE, a Cytoscape plugin-in, which indicating important and potential biomarkers that contributed to the development and progression of cancers with MAP3K8 (Figure 9B).

Functional enrichment analyses of MAP3K8 using the GO and KEGG approaches

GO and KEGG signal pathway analysis were conducted to predict the functional enrichment information of interactive genes of MAP3K8 using the Metascape website. MAP3K8-related genes were involved in functions of BP, CCs, and MFs. We found that I-kappaB kinase/NF-kappaB signaling, activation of protein kinase activity, and response to tumor necrosis factor had significant regulation by the gene clusters (Figure 10A-C). Significant KEGG enrichment analyses showed in T cell receptor signaling pathway, MAPK signaling pathway, central carbon metabolism in cancer, oxytocin signaling pathway, axon guidance, and microRNAs in cancer. The findings revealed that MAP3K8 serves an essential role in regulation of T cell, MAPK signaling pathway, and several other important metabolic processes (Figure 10D), which was further verified by interactive networks of the enrichment terms of GO and KEGG (Figure 11A-B).

Discussion

This study conducted 453 unique analyses spanning 20 kinds of cancers from the ONCOMINE Platform along with 33 cancer types from the GEPIA database using TCGA and the GTEx projects and identified that MAP3K8 had a significantly low expression profile in most analyzed human cancers. However, MAP3K8 expression level was affected by clinical parameters such as tumor grade, patient age, and histology. We further performed survival analysis of MAP3K8 via three online databases, which reflects that prognostic values of MAP3K8 vary depending on tumor types. High expression of MAP3K8 are associated with better clinical outcomes on OS in MESO and SKCM, while KIRC and THYM patients with high expression of MAP3K8 showed poorer clinical performance on OS. MAP3K8 has a complex role in cancers and it is possible that each cancer type present tumor-specific biomarkers and characteristic genetic backgrounds. It is not surprising that each cancer has a special molecular landscape with numerous interactional networks. In this study, we sought to explore the PPI networks of MAP3K8, using GeneMANIA and Cytoscape. Our results revealed a set of proteins mainly including REL, RELA, TNIP2, NFKB1, NFKB2, KSR2, NFKBIA, and p105, which was significantly associated with MAP3K8 in cancers. These proteins were involved in critical cellular processes that play a tumor-suppressive role or a pro-tumorigenic role in cancers, yet still lack substantial researches to deeply verify their context-dependent roles and clinical values in human cancer.

MAP3K8 gene encodes two protein isoforms that are identified as serine/threonine protein kinase and localized in cytoplasm [4, 5]. The protein was found to promote the production of tumor necrosis factor-alpha (TNF- α) and interleukin-2 (IL-2) during T lymphocyte activation and can also activate both the MAPK and c-Jun N-terminal kinase (JNK) pathways, which were particularly important for inflammatory responses [4]. MAP3K8 has been identified as an indispensable modulator of immune responses that conveys inflammatory signals, modulating functions of inflammatory cells. Yet, inflammatory responses play decisive roles at different stages of tumor development and also affects immune surveillance and responses to anti-cancer therapy [22]. Tumor-infiltrating immune cells engage in an extensive and dynamic crosstalk with cancer cells, and some of the principal mechanisms that mediate this dialog have

been uncovered. What is the theme of this study, however, is that care has to be taken in touching on the relationships between MAP3K8 and human cancers. Although MAP3K8 was originally recognized as an oncogene since its discovery in 1991, genetic sequence analyses identified rare MAP3K8 mutations which is much less than altered expression and abnormal activation in human cancers [6]. Previous studies have found that overexpression and increased activation of MAP3K8 are main events associated with increased tumorigenesis including initiation, promotion and progression as well as poor prognosis [6, 23]. In addition, reduced MAP3K8 expression is also related to poor prognosis and tumor aggressiveness in some cancers such as non-small cell lung cancer (NSCLC) [24, 25]. Hence, we performed this study to investigate the clinical value and distinguished function of MAP3K8 in human cancers based on bioinformatic tools.

Three databases were employed to elucidate expression profile of MAP3K8. The ONCOMINE and UALCAN databases showed that MAP3K8 was up-regulated in KIRC compared with paired normal tissues, which was inconsistent with the results of the GEMIA database. However, Yusenko et al. have identified loss of chromosome 10, the genomic location for MAP3K8 gene, as one of the discriminating alterations between chromophobe renal cell carcinoma (RCC) and benign renal oncocytoma (RO), indicating transcriptional regulations of MAP3K8 gene as a main cause of overexpression [26]. Given the results that grade 4 KIRC showed higher MAP3K8 level than grade 3 KIRC, MAP3K8 could contribute to KIRC progression. Furthermore, elevated MAP3K8 activity in preclinical KIRC models promoted tumorigenesis and metastatic ability through activating MAPK pathway and cross-talk with CXCL12/CXCR4-directed chemotaxis and chemo-invasion [12]. In addition, higher level promoter methylation of MAP3K8 was also found in KIRC and related to tumor grade. Accordingly, abnormal activation of MAPK pathway and DNA methylation could partly elucidate the detailed mechanism of MAP3K8-driven oncogenic events. Our comprehensive survival analyses from the three databases revealed that enhanced expression of MAP3K8 indicated poor OS in KIRC patients. This result is expected for the KIRC, which was the only cancer that has significant prognostic value on MAP3K8 across three databases. These observations suggested that MAP3K8 has potentials to be a prognostic indicator and needs to be further investigated to determine its function and impacts on KIRC progression.

The ONCOMINE database failed to identify differential expression of MAP3K8 in THCA and THYM. Deeper exploration using UALCAN database found that MAP3K8 expression level was down-regulated in all histological subtypes of THCA compared with paired normal tissues, and promoter methylation of MAP3K8 was more commonly seen in stage 4 THCA compared with stage 2 THCA. However, we mined few information about MAP3K8 expression in THYM in the selected websites. In contrast, previous studies have found elevated MAP3K8 activity in THCA and THYM [5]. This result is similar to that found in survival analyses of THCA, in which high-level expression of MAP3K8 was associated with better clinical outcomes in GEPIA database but with poorer clinical outcomes in UALCAN database. Our results could be partly explained by published results by Giani et al., in which MAP3K8 inhibitor restored the efficacy of vemurafenib in thyroid cancer stem cells (CSCs) that harbored BRAF V600E, a common mutation in MAPK pathway, and high-level expression of MAP3K8 [27]. Indeed, as the results demonstrated, not only are the signature of good clinical outcome, but in some cases, high-level

expression of MAP3K8 may be a useful marker to predict drug resistance. There may be other considerable reasons to explain these variations, such as our failure to comprehensively dig genetic alterations of these cancers directly using TCGA database and GEOx, technical improvements in detecting genomic changes, and diversity of tumor samples. Interestingly, given the contradictory situations, we still found that high-level expression of MAP3K8 in THYM indicated poor clinical outcome, using DriverDBv3 and UALCAN databases. Collectively, our results could provide some valuable information for future researches of THCA and THYM.

In GEPIA and UALCAN databases, the expression level of MAP3K8 was lower in SKCM than that in paired normal tissues and affected by patient age. Survival analyses found that high-level expression of MAP3K8 indicated better clinical outcome of SKCM. However, some oncogenic mutations may alter the positive value of high-level MAP3K8 expression in SKCM [8, 28]. The serine/threonine kinase B-RAF mutation (BRAF V600E) is frequently detected in SKCM, which predicts a successful response of RAF and MEK inhibitors in clinical trials. However, efficacy to these targeted therapeutics are frequently defeated by acquired resistance which can be driven by MAP3K8 activation because MAP3K8 activates ERK primarily through MEK-dependent mechanisms that do not require RAF signaling [8]. Johannessen et al. further identified that the use of MEK and BRAF inhibitors in combination can override drug resistance [28]. In addition, Newman et al. found that MAP3K8 rearrangements are the most common genetic event in spitzoid melanoma and present in adult melanomas, and could be amenable to MEK inhibition [8]. MAP3K8 expression are higher in both TYCA and SKCM than in normal tissues. Our results suggest that MAP3K8 will be a valuable molecular marker and target for the treatment of BRAF V600E-positive TYCA and SKCM. We also found that metastatic samples of SKCM showed higher level promoter methylation of MAP3K8 than primary samples, which could be provided as a clinical parameter to predict metastatic potential of melanoma cells. For MESO, high MAP3K8 expression also predict a better OS, but the detailed mechanisms that MAP3K8 functions in MESO need further researches.

Our study constructed the interaction network of MAP3K8-associated genes. MAP3K8 was found to be involved in various biological processes through GO and KEGG analyses, mainly including immune cell function and MAPK signaling pathway. Innate immune system detecting pathogen-associated molecules by Toll-like receptors (TLRs) that expressed on various immune cells is influenced by MAP3K8. For example, activation of the MAP3K8/MEK/ERK pathway in macrophages not only regulates the production of cytokines but also the cellular response to TNF, IL-1b and CD154, the CD40 ligand, suggesting that MAP3K8 may have a broader role in inflammatory signal transduction in innate immune cells and could be exploited as anti-inflammatory drug target [29, 30]. These observations, along with the identified functions in MAPK pathway, give us a great interest to establish the potentials of MAP3K8 on both inflammation and malignancy. However, there are some limitations to this study. Different online databases may produce different results due to various sample size and source. We still need fundamental researches, pre-clinical and clinical studies to verify the bioinformatics analysis findings of MAP3K8.

Conclusions

Our analyses using several databases identified expression level and prognostic value of MAP3K8 in distinct types of cancer. The results revealed that MAP3K8 overexpression was correlated with improved survival in MESO and SKCM, and with damaged survival in KIRC and THYM, reemphasizing the potential for identifying predictive biomarkers and therapeutic targets focused on MAP3K8 and the MAPK pathway. Our data also revealed several enriched functions mainly including immune cell function and MAPK signaling pathway that significantly associated with the MAP3K8 gene. This study reminds us of the potential roles of MAP3K8 in tumorigenesis and as a prognostic biomarker in certain human cancers. Moreover, continuous studies will be required to power the discoveries of MAP3K8 in this study.

Abbreviations

MAPK: Mitogen-activated protein kinase; MAP4K: MAPK kinase kinase kinase; MAP3K: MAPK kinase kinase; MAP2K: MAPK kinase; MAPKAPK: MAPK-activated protein kinases; Pin1: Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1; CXCL12: C-X-C motif ligand 12; DEGs: Differently expressed genes; OS: Overall survival; DFS: Disease-free survival; TCGA: the Cancer Genome Atlas; GTEX: Genotype-Tissue Expression; PPI: Protein-protein interaction; GO: Gene Ontology; BP: Biological processes; CC: Cellular component; MF: Molecular function; KEGG: Kyoto Encyclopedia of Genes and Genomes; ACC: Adrenocortical carcinoma; LUAD: Lung adenocarcinoma; LUSC: Lung squamous cell carcinoma; SKCM: Skin cutaneous melanoma; KIRC: Kidney renal clear cell carcinoma; THCA: Thyroid carcinoma; KM: Kaplan-Meier; CESC: Cervical squamous cell carcinoma; KIRP: Kidney renal papillary cell carcinoma; LGG: Brain lower grade glioma; UVM: uveal melanoma; MESO: mesothelioma; THYM: Thymoma; TNF- α : Tumor necrosis factor-alpha; IL-2: interleukin-2; JNK: c-Jun N-terminal kinase; NSCLC: Non-small cell lung cancer; RCC: Renal cell carcinoma; RO: Renal oncocytoma; CSCs: Cancer stem cells; TLRs: Toll-like receptors.

Declarations

Acknowledgements

Not applicable.

Authors' contributions

JH was responsible for study design and article writing. YC, HY, and LZ were responsible for figures editing. RA, and YX were responsible for proofreading. All authors read and approved the final manuscript.

Funding

The study was funded by the 2019 Youth Development Project of The First Affiliated Hospital of Xi'an Jiaotong University [2019QN-20] and the National Natural Science Foundation of China [No.81972428].

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

As this is a bioinformatics analysis of data mining, ethics is not applicable.

Consent for publication

Not applicable.

Competing interests

The authors report no conflicts of interest in this work.

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Figures

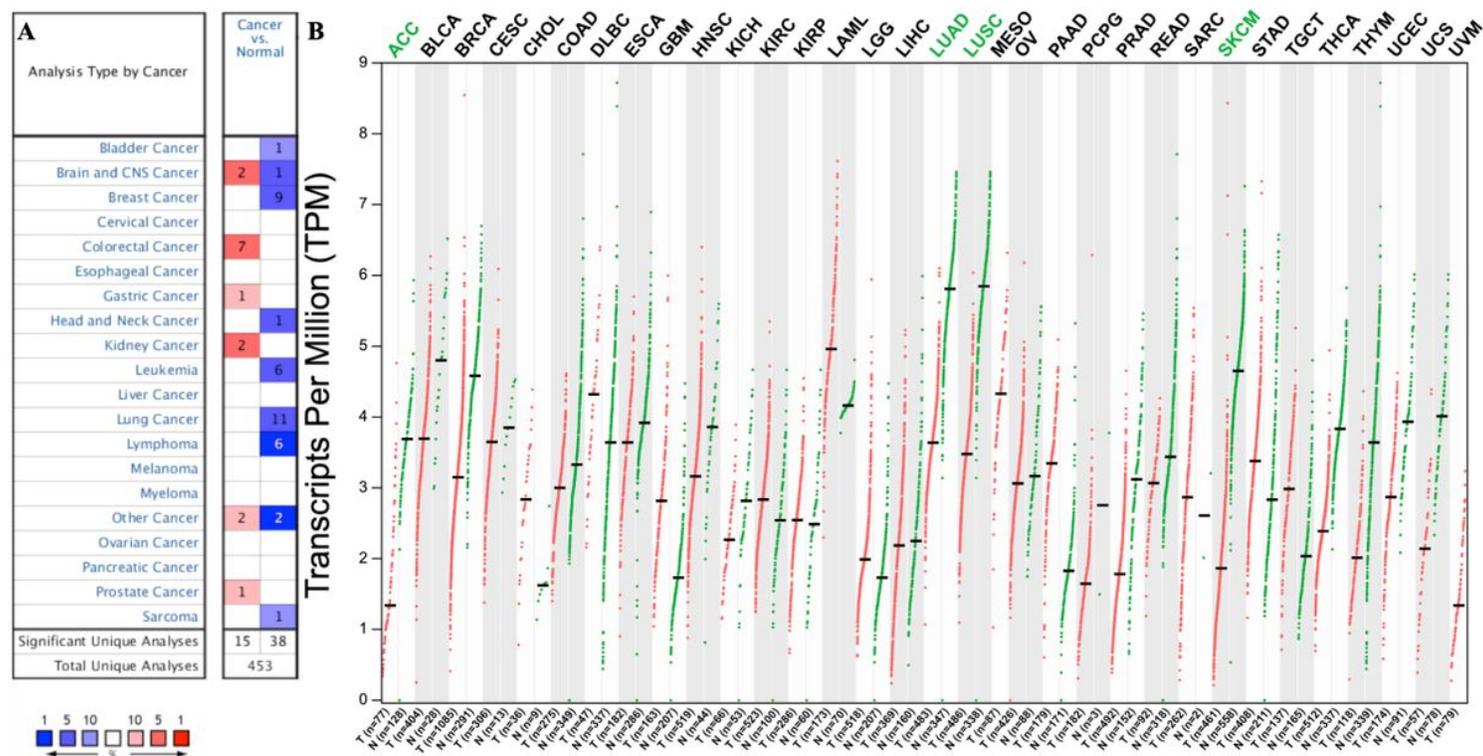


Figure 1

MAP3K8 expression level in different human cancers. (A) Unique analyses of MAP3K8 mRNA expression in different cancers samples compared with paired normal tissues in the Oncomine database; (B) MAP3K8 expression profile across all tumor samples and paired normal tissues determined by GEPIA.

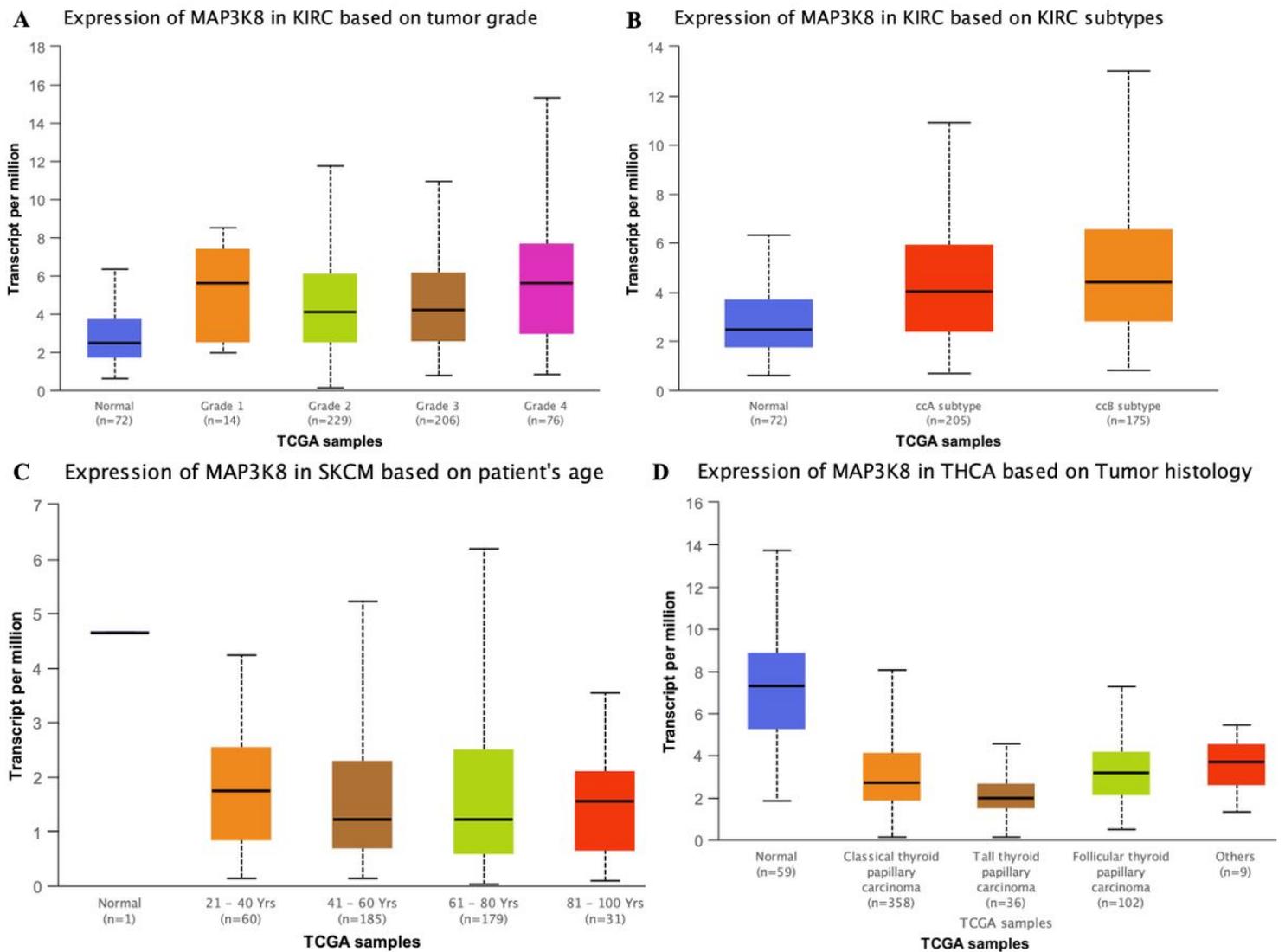


Figure 2

Box plots indicating MAP3K8 expression levels in tumors based on subgroups using UALCAN. (A) Expression level of MAP3K8 in different tumor grade of KIRC; (B) Differential expression level of MAP3K8 in KIRC subtypes; (C) Differential expression level of MAP3K8 in SKCM based on patient's age; (D) Differential expression level of MAP3K8 in THCA based on tumor histology.

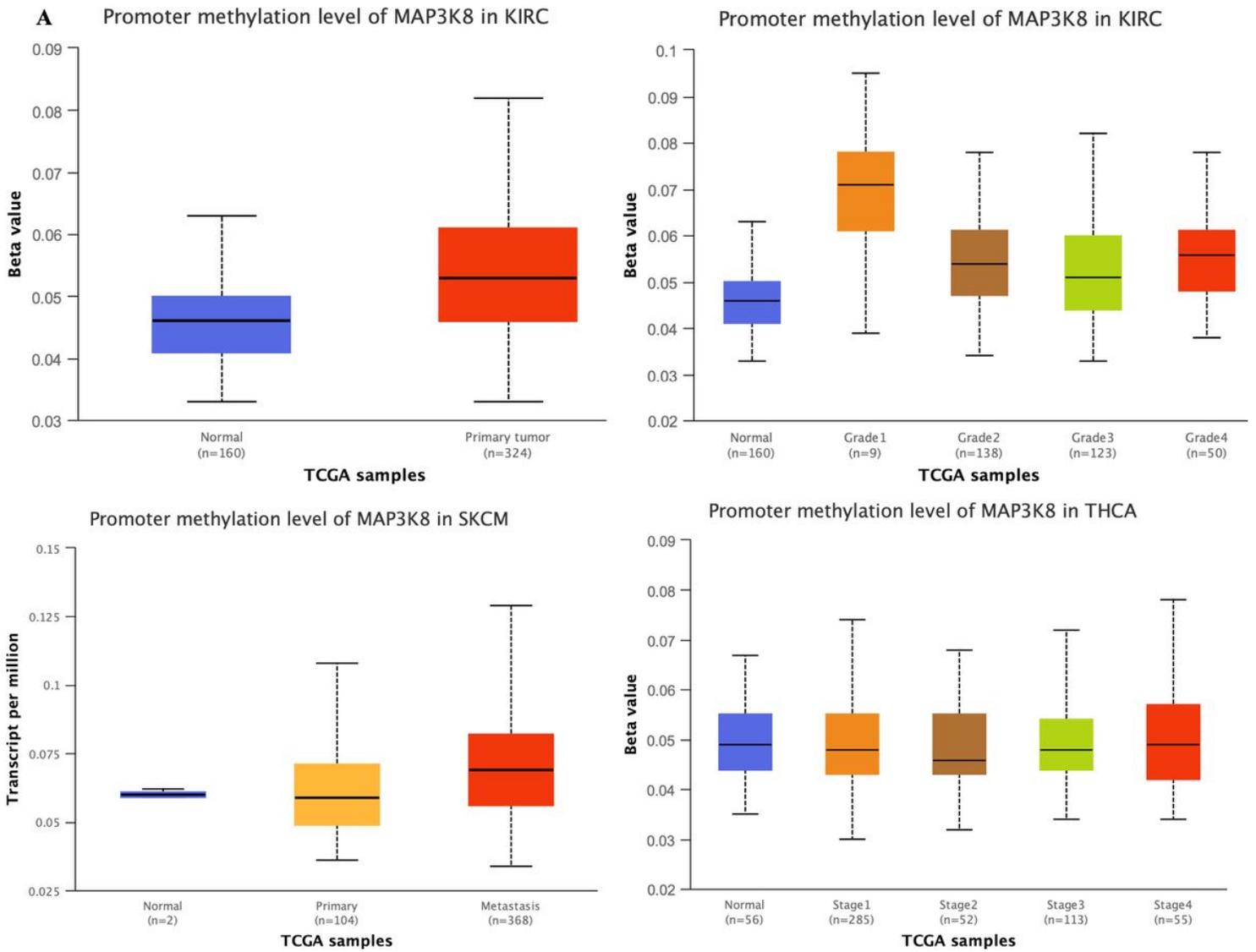


Figure 3

Promoter methylation level of MAP3K8 in defined cancer types using UALCAN. (A) Promoter methylation level of MAP3K8 in normal and KIRC tissues; (B) Promoter methylation level of MAP3K8 in different KIRC grades; (C) Promoter methylation level of MAP3K8 in primary and metastatic SKCM tissues; (D) Promoter methylation level of MAP3K8 in different THCA stages.

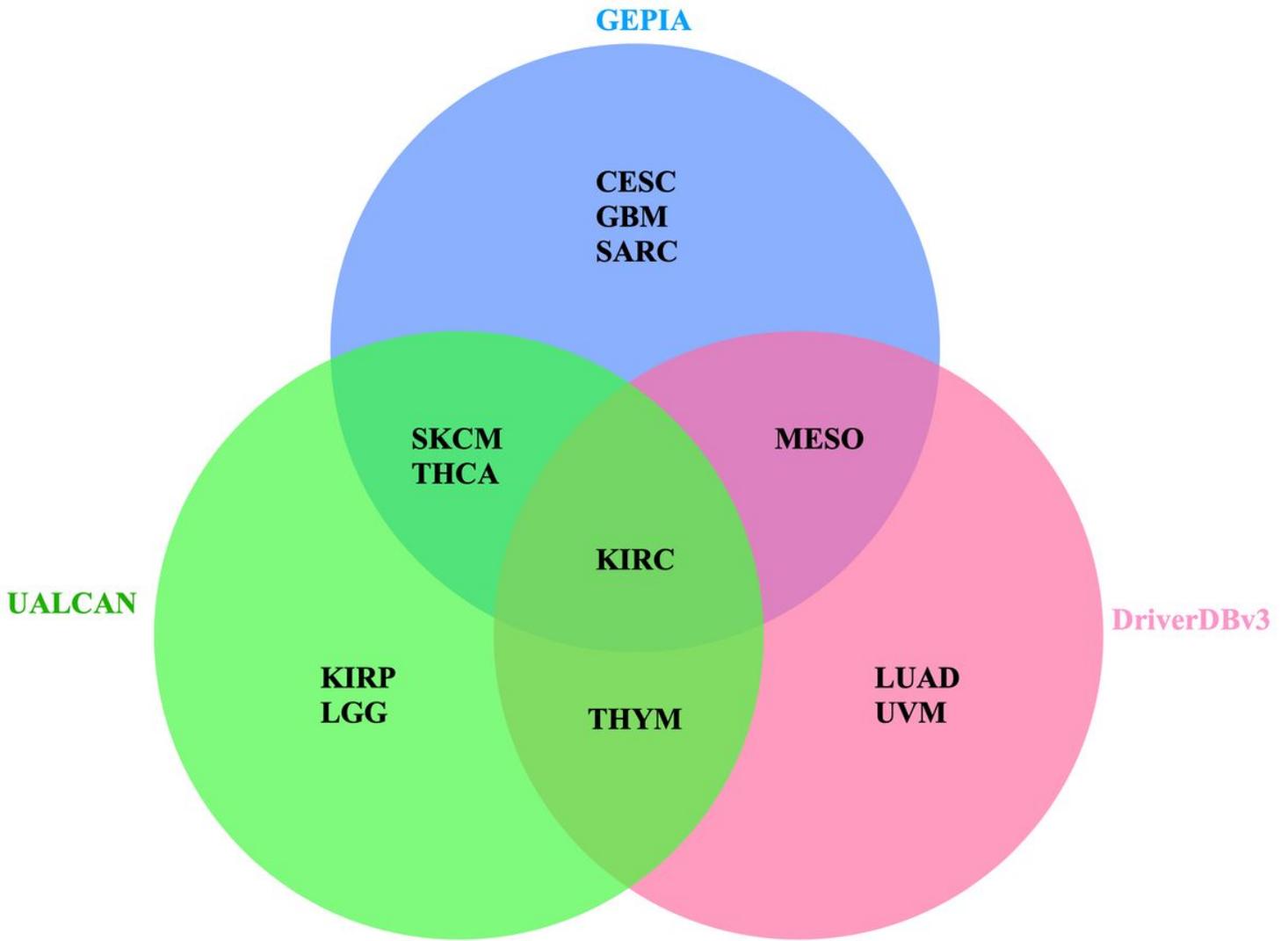


Figure 4

Wayne diagram for comprehensive analysis of MAP3K8 expression in GEPIA, UALCAN, and DriverDBv3.

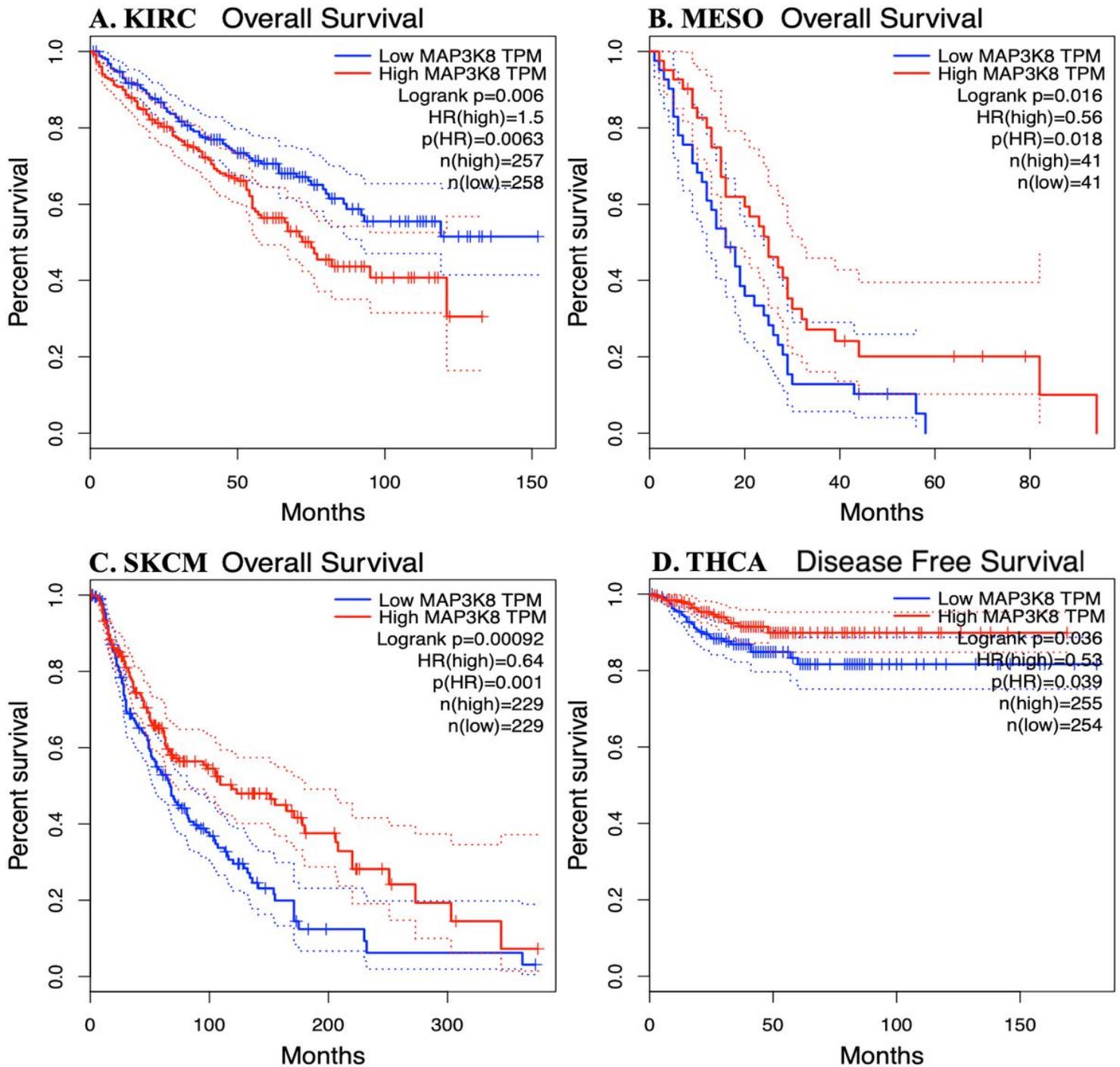


Figure 5

KM curves comparing high and low expression of MAP3K8 in different cancers in the GEPIA database. (A) OS survival curve of KIRC; (B) OS survival curve of MESO; (C) OS survival curves of SKCM; (D) DFS survival curves of THCA.

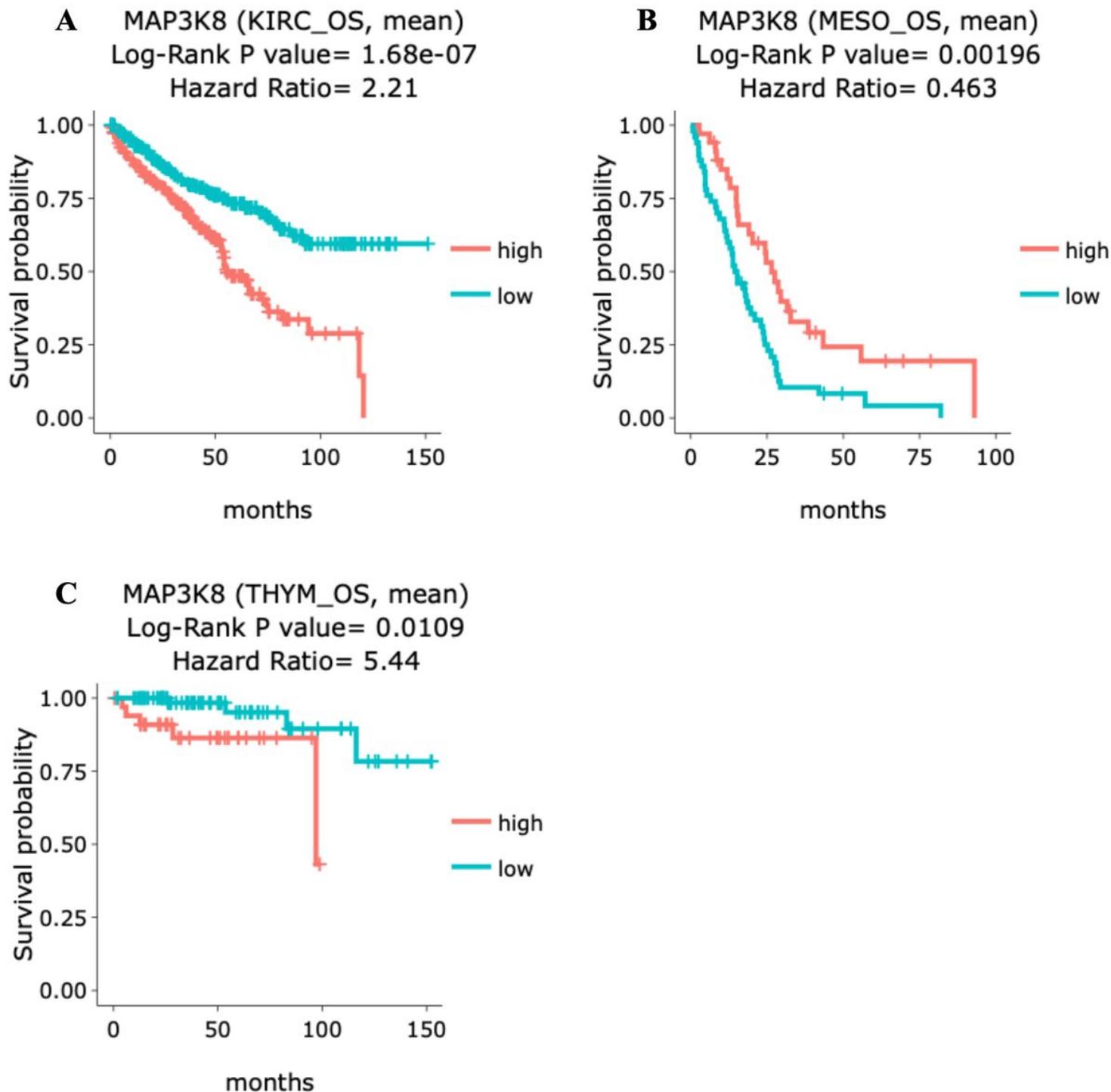


Figure 6

Prognostic information of the MAP3K8 in DriverDBv3 database. (A) OS survival curve of KIRC; (B) OS survival curve of MESO; (C) OS survival curves of THYM.

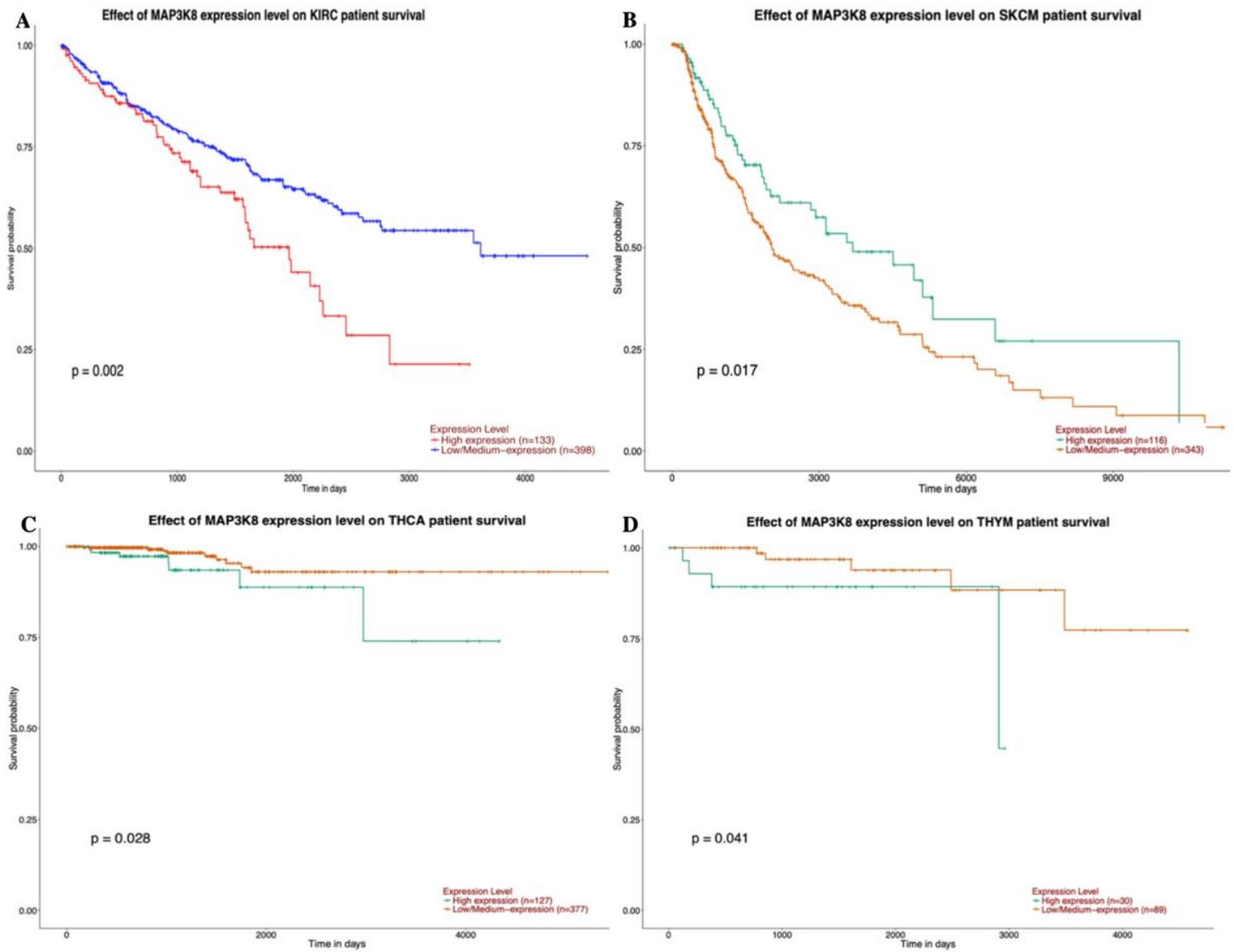


Figure 7

The effect of MAP3K8 expression level on OS in KIRC (A), SKCM (B), THCA (C), and THYM (D), respectively.

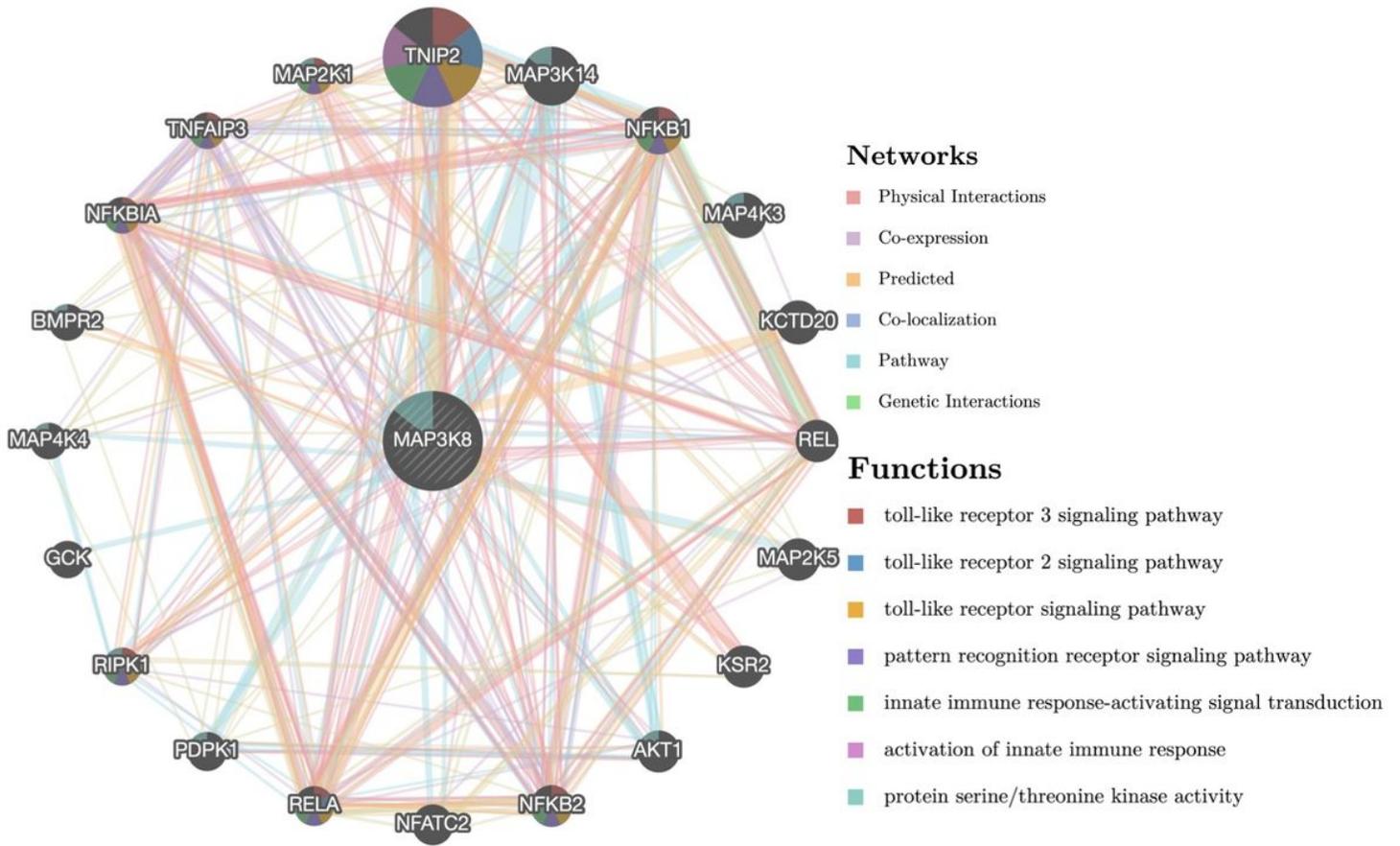


Figure 8

PPI network of MAP3K8 using GeneMANIA.

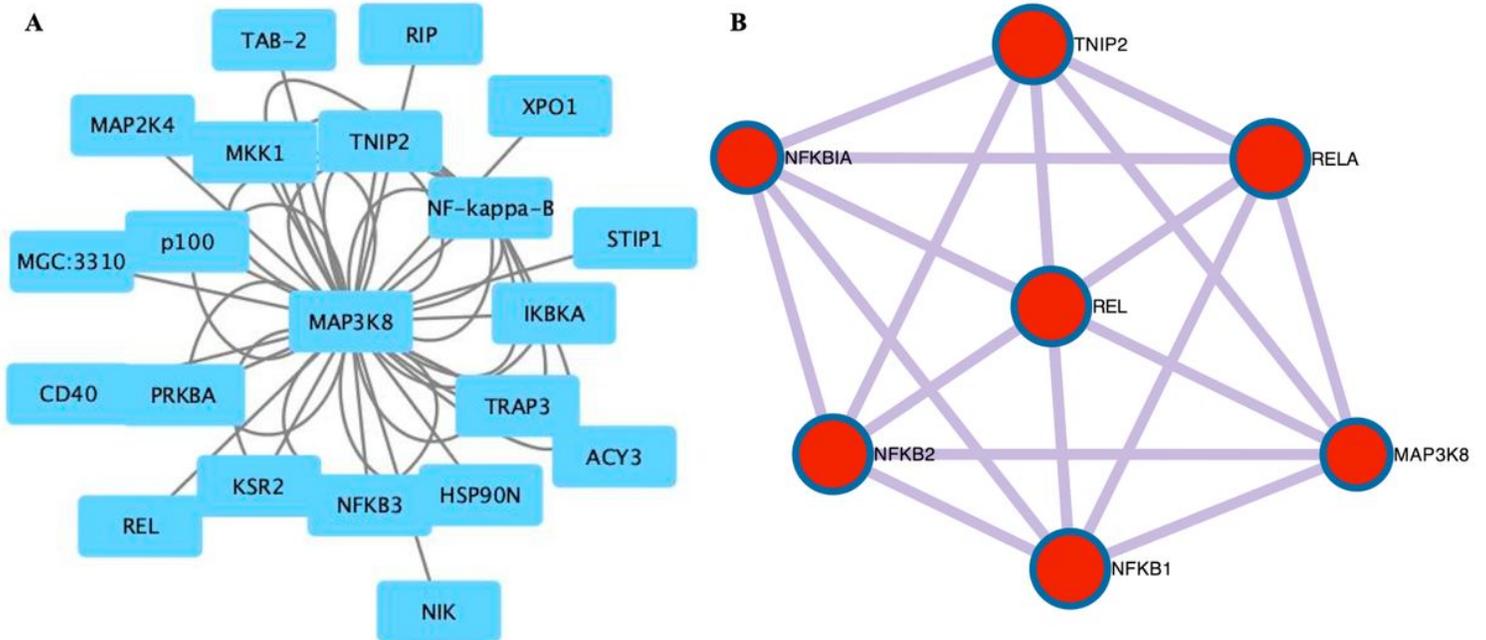


Figure 9

PPI network of MAP3K8-associated genes. (A) PPI network of MAP3K8-correlated genes constructed by Cytoscape. (B) The core modules of genes and enriched terms associated with MAP3K8 through MCODE.

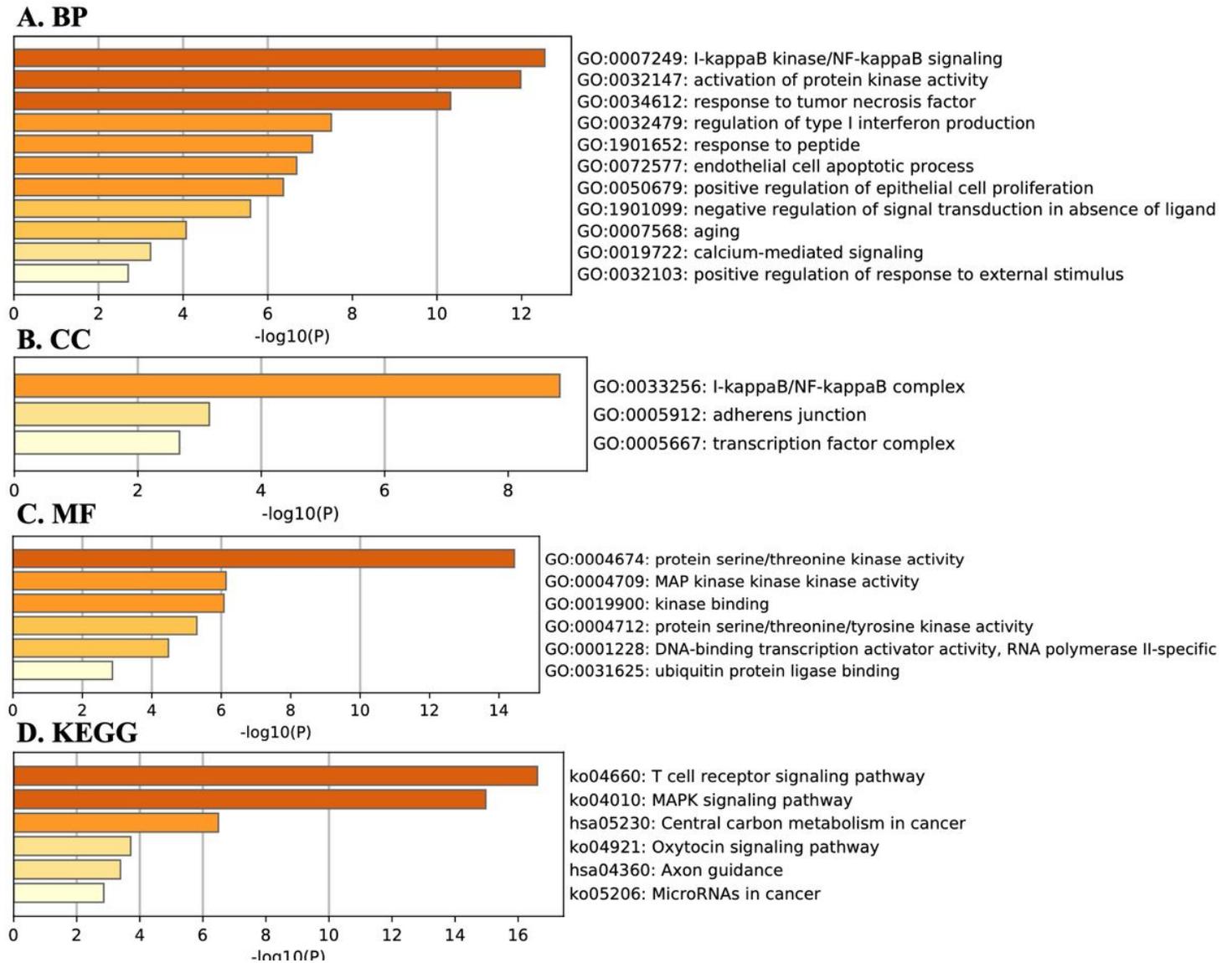


Figure 10

Heatmaps of GO analysis including BP (A), CC (B) and MF (C), and KEGG analysis (D) across MAP3K8 and other interactive gene lists. Orange is the enrichment terms and colored by P values.

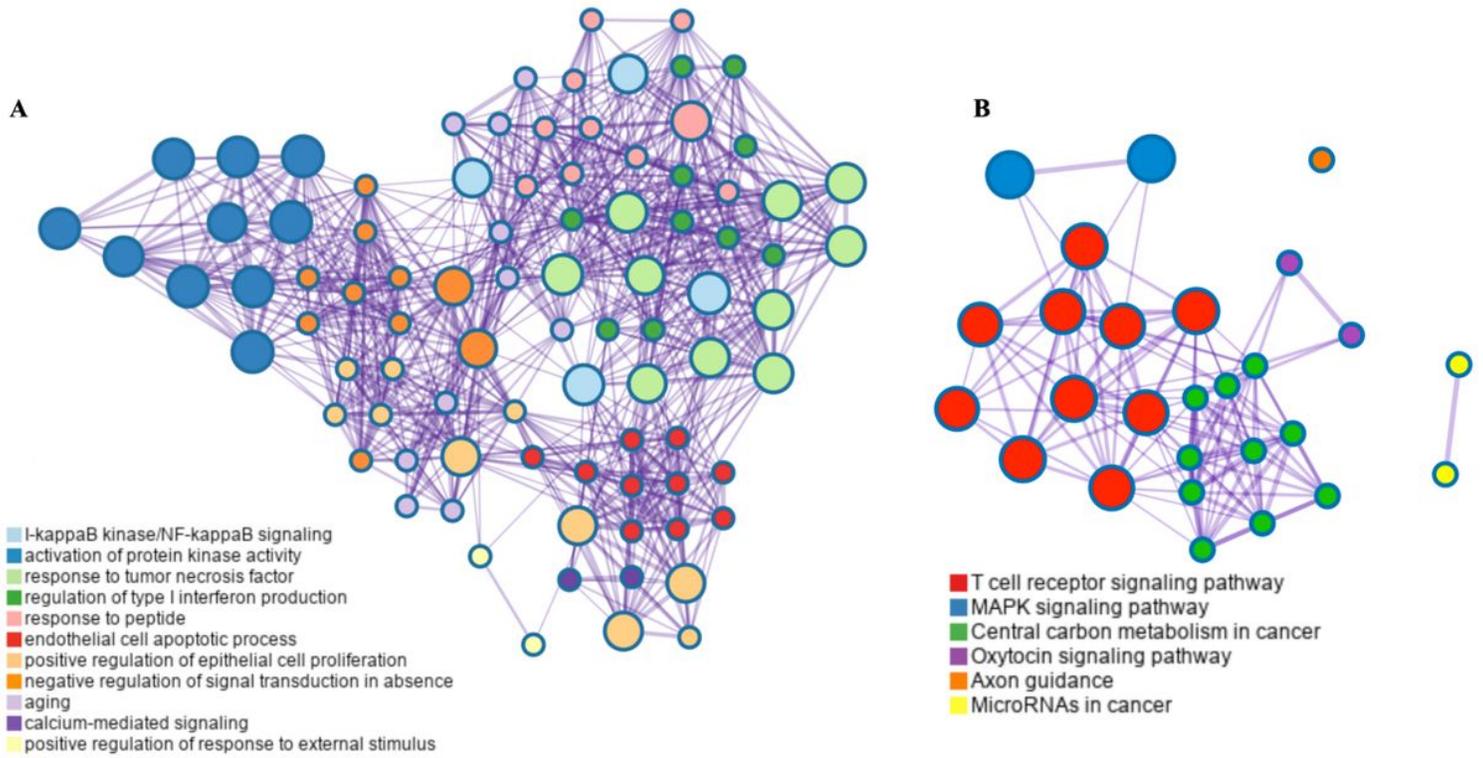


Figure 11

Interactive networks of the enrichment pathways of MAP3K8 correlated genes. (A) Enrichment pathways of MAP3K8 from BP; (B) Enrichment pathways of MAP3K8 from KEGG.