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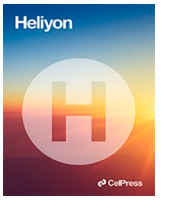

Research article

A bird's eye view of the potential role of NFKBIA in pan-cancer

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ABSTRACT

In the 21st century, cancer remains a serious threat to people's health and has become a prominent public health problem. NFKBIA is involved in the pathological process of many diseases including cancer, but its specific role in pan-cancer has not yet been fully elucidated. This study aims to deepen the understanding of cancer pathology by analyzing the potential functions of NFKBIA in pan-cancer. We used TCGA data to analyze differences of expression of NFKBIA in pan-cancer. We explored the prognostic value, clinical relevance, immune relevance, potential biological function, and diagnosis and treatment value of NFKBIA in pan-cancer through bioinformatics analysis. This study found that in pan-cancer, NFKBIA exhibits differences in expression, which correlate with the prognosis, diagnosis, treatment value and clinical and immune parameters. We have identified that Aspirin, Astaxanthin and Bardoxolone methyl are expected to play a potential therapeutic role in pan-cancer. The results of this study will help to improve our understanding of the role and potential mechanism of NFKBIA in cancer pathology, which may provide guidance for cancer-related research and clinical diagnosis and treatment.

1. Introduction

In the 21st century, cancer remains a serious threat to people's health and has become a prominent public health problem. According to statistics, there were nearly 20 million new cancer cases and 9.7 million cancer deaths worldwide in 2022 alone. According to demographics-based predictions, the number of new cancer cases will be expected to reach a terrifying 35 million by 2050 [1]. Despite the continuing improvement of cancer diagnosis technology and the development of new treatment methods, it is still difficult to meet the needs of many cancer patients. In order to further improve the efficacy of cancer diagnosis and treatment, it is important to decipher the pathological mechanisms of carcinogenesis.

NFKB inhibitor alpha (NFKBIA) is a member of the NF-kappa-B (NF-kB) inhibitor family. NFKBIA protein interacts with REL dimers to decrease inflammation by inhibiting NF-kB/REL complexes. In resting cells, NF-kB is present in the cytoplasm in an inactive state, bound to NFKBIA protein [2]. The latter is phosphorylated following the induction of IkB kinase (IKK), resulting in its degradation, which in turn causes the translocation of activated NF-kB to the nucleus to initiate the transcription of genes involved in processes such as inflammation, apoptosis, angiogenesis, migration, and cell proliferation [3,4]. With the deepening of research in the field of oncology, cancer immunotherapy has begun to take center stage by facilitating the ability of the host to generate ongoing anti-tumor

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immune responses [5]. In this context, NFKBIA has been found to be closely related to this immune response [6,7]. Pan-cancer analysis can collect consistent TCGA data sets across tumor types and platforms, and guide cancer-related research and clinical treatment through integrated analysis of gene function [8]. Given that pan cancer analysis creates infinite possibilities for improving the diagnosis and treatment of cancer, we can reveal the potential value of NFKBIA in cancers with pan-cancer analysis.

In the present study, we re-analyzed TCGA data and found differences in the expression of NFKBIA in many different cancers. We then comprehensively analyzed correlations of NFKBIA expression with the prognosis, diagnosis, treatment outcome and clinical and immune status. The results of this study will help to improve our understanding of the role and potential mechanism of action of NFKBIA in cancer pathology, which may provide guidance for cancer-related research and clinical diagnosis and treatment.

2. Materials and methods

2.1. Biological notes on NFKBIA

In order to better understand NFKBIA, we first used Ensembl [9] (https://www.ensembl.org), a powerful genome browser, to comprehensively annotate NFKBIA in the human genome. The Human Protein Atlas [10] (https://www.proteinatlas.org/), a project that uses various omics technologies to integrate proteins in human cells, tissues and organs, was used to explore the location of NFKBIA in human cells. In order to better explore the function of NFKBIA in cells, we identified the subcellular localization of NFKBIA protein in cells using The Human Protein Atlas database. The database only includes the detection results of three cell lines (A-431, U-2 OS and U-251 MG). We have gained a general understanding of the localization of NFKIBA protein in cells through database data. STRING [11] (https://string-db.org/), a database that can identify known protein relationships from more than 24 million proteins and predict potential interactions between proteins, was used to identify and construct a NFKBIA-related PPI network. We set the maximum number of interactors to no more than 20. Reactome [12] (https://reactome.org/) is an open source pathway database that can visualize, interpret and analyze pathway information. We identified the pathways related to NFKBIA through the Reactome program to gain a deeper understanding of its biological functions.

2.2. NFKBIA expression in pan-cancer

The canSAR database [13] (https://cansarblack.icr.ac.uk/) collects and integrates a large amount of multidisciplinary data, which is widely used in oncology-related research. Oncomine [14] (https://www.oncomine.org/), a large database covering more than 700 datasets, can perform efficient cancer-related analysis. We analyzed the expression of NFKBIA in pan-cancer through the canSAR and Oncomine databases. In order to more comprehensively identify the level of expression of NFKBIA in pan-cancer, we downloaded the RNA expression data of 33 cancers from the TCGA database (https://www.cancer.gov/), and extracted and visualized the expression of NFKBIA in different cancers through the use of Perl language (https://www.perl.org/) and R language (https://www.r-project.org/). The Human Protein Atlas was used to identify the expression of NFKBIA protein in different cancers and extract representative pathological images [15].

2.3. Clinical relevance of NFKBIA

We applied the Kaplan-Meier (KM) method, a widely used survival analysis technique, to analyze the potential prognostic value of NFKBIA in pan-cancer [16]. We downloaded patient survival data from the TCGA database, and performed KM survival analysis through the three R packages survival, limma and survminer. We conducted four survival analyses, namely overall survival (OS), disease-free interval (DFI), disease-specific survival (DSS) and progression-free interval (PFI) to explore the potential value of NFKBIA for the prognosis of different cancers. We also applied Cox proportional hazards regression model (Cox model) survival analysis, regarding NFKBIA as a continuous variable, in order to compare the effects of NFKBIA on survival time and survival status in different cancers [17]. We show the effects of NFKBIA on OS, PFI, DSS and DFI of different cancers in the form of forest plots, with the help of limma, forestplot and survival packages. Furthermore, we conducted a preliminary analysis of the pan-cancer-related clinical data in the TCGA database, and carried out an assessment of the impact of NFKBIA on the patient's race, gender, age, and tumor type, stage, and status through two program packages, ggpubr and limma.

2.4. Analysis of factors related to tumor immunity

In order to explore the potential impact of NFKBIA on immunity in pan-cancer, we performed an analysis of factors known to be relevant for tumor immunity. Microsatellite instability (MSI) can be used for cancer screening, diagnosis and prediction of prognosis. Tumor mutational burden (TMB) reflects the quantity of tumor cell mutations in different cancers [18]. We used the Perl language to preprocess TCGA data, and the fmsb package to explore the impact of NFKBIA on MSI and TMB. The tumor microenvironment (TME) is highly influential on tumor immunity [19]. Stromal cells, which can inhibit the infiltration of immune cells into tumors, are an important non-cancer component in the TME [20]. Therefore, we explored the potential effects of NFKBIA on stromal cells and immune cells in the TME through the five R packages ggExtra, ggpubr, limma, estimate and ggplot2. Normal function of immune cells is of great significance for maintaining the stability of the TME [21]. Therefore, identifying the key changes of immune cells in tumors is very important for tumor-related research and treatment. In this study, we analyzed the correlation between NFKBIA and 22 specific immune cells through R software [22]. Immune checkpoints are expressed by immune cells, which regulate immunity in the body, and

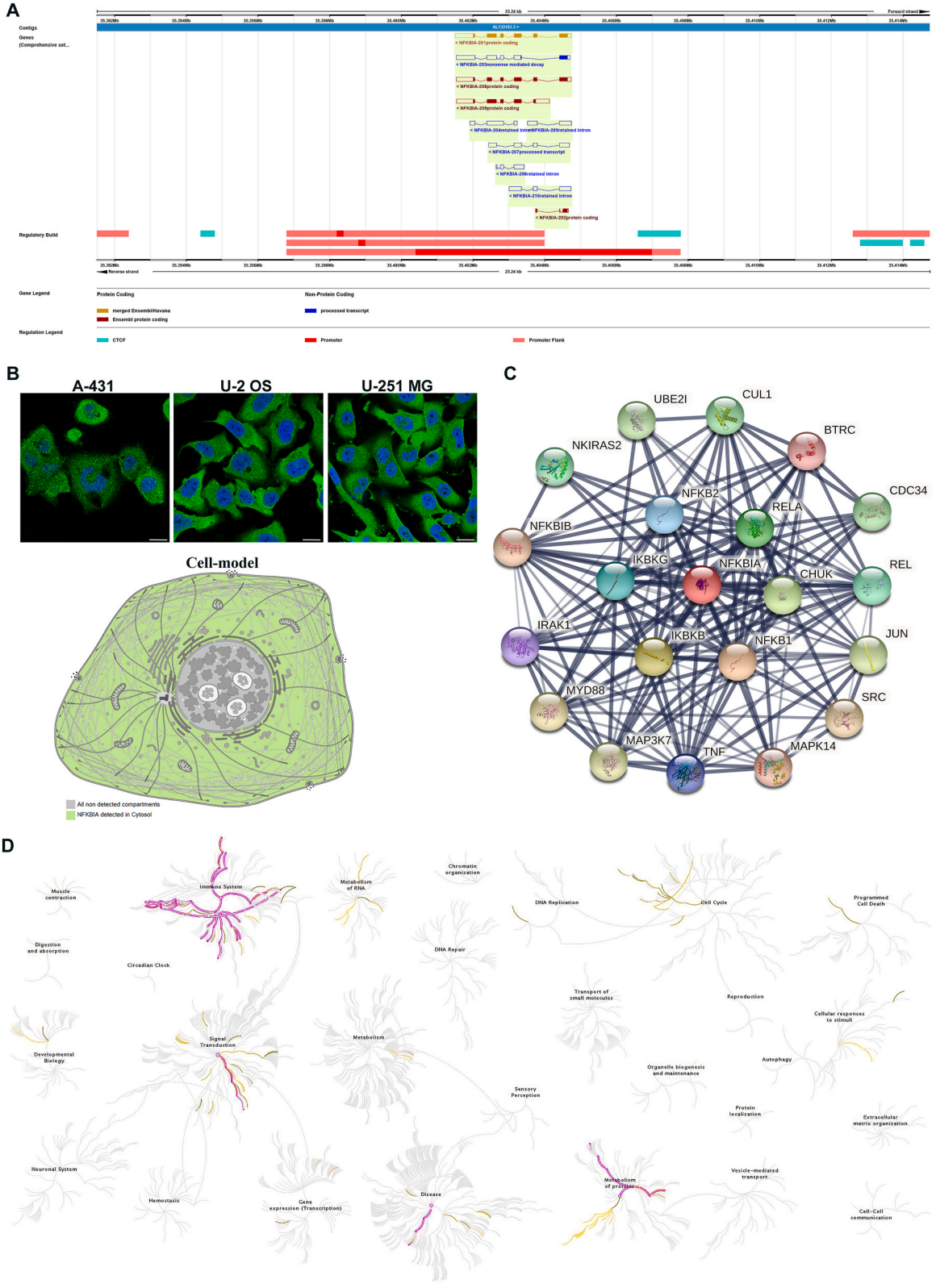

Fig. 1. Biological notes of NFKBIA. A. Gene annotation of NFKBIA. B. The location of NFKBIA in human cells. Scale bar = 20 μm. (The Human Protein Atlas) C. The protein-protein interaction (PPI) network of NFKBIA. D. The signal pathways related to NFKBIA.

can be leveraged to improve the effect of cancer treatment through their specific inhibition [23]. We further analyzed the potential correlation between NFKBIA expression and 47 common immune checkpoints through R software, in order to explore the potential value of NFKBIA in tumor treatment.

2.5. Gene set enrichment analysis (GSEA)

In order to study the potential role of NFKBIA in biological processes, we conducted Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) enrichment analysis through the GSEA database (https://www.gsea-msigdb.org/) and R software [24]. We focused on the 5 enrichment items most relevant to NFKBIA in pan-cancer.

2.6. Receiver operating characteristic (ROC) analysis

ROC analysis is a common method used to analyze diagnostic values, and the area under the ROC curve (AUC) can be used to predict the effectiveness of the analysis. In this study, we analyzed the potential diagnostic value of NFKBIA for pan-cancer in the TCGA database through R software [25].

2.7. Potential drug selection

In view of the important role of NFKBIA in pan-cancer, we analyzed drugs potentially targeting NFKBIA and the drug sensitivity changes related to NFKBIA mutations through the DrugBank database (https://go.drugbank.com/) [26] and the COSMIC database (https://cancer.sanger.ac.uk/) [27], respectively.

2.8. Gene mutation analysis

The cBioPortal for Cancer Genomics database (https://www.cbioportal.org/) was used to collect NFKBIA related gene mutation data in TCGA tumors [28].

2.9. Statistical methods

We used R software and Perl software for data processing and illustrations. The Wilcoxon test was used to assess differences in NFKBIA expression. Pan-cancer prognostic differences associated with NFKBIA were analyzed using the log-rank test. The analysis of NFKBIA and immune-related factors was by the Spearman test. $P \leq 0.05$ was considered to be statistically significant. $^{*}P \leq 0.05$, $^{**}P \leq 0.01$, $^{***}P \leq 0.001$.

3. Results

In order to present our study more clearly, we provide a flow chart to show our approach (S-Fig. 1).

3.1. Biological notes on NFKBIA

In order to understand NFKBIA more comprehensively and accurately explore its potential functions in pan-cancer, we used database tools to annotate NFKBIA biologically to facilitate the interpretation of its features. First, we comprehensively annotated the NFKBIA gene in the human genome. The NFKBIA gene has 10 splice variants and is related to 5 phenotypes (Fig. 1A). Second, we found that NFKBIA protein is mainly located in the cytoplasm through the detection results of A-431, U-2 OS and U-251 MG cell lines included in the Human Protein Atlas database, but a small amount of NFKBIA protein is also recognized to exist in the plasma membrane in U-2 OS cell lines. The function, metabolism, and interactions of proteins produced by gene expression are closely related to their subcellular localization. Mature proteins must be located in specific subcellular structures in order to perform their correct and stable biological functions. If the positioning deviates, it will have a significant impact on cell function and even life. The deviation of NFKBIA localization in cells may lead to the occurrence and development of cancers. (Fig. 1B). Third, we explored proteins interacting with NFKBIA, and extracted the 20 most closely related in order to construct a PPI network (Fig. 1C). Finally, we explored the biological processes in which NFKBIA participates. We recognized that NFKBIA is widely involved in many biological processes such as functions of the immune system, in signal transduction, and in protein metabolism, and is closely involved in many disease processes (Fig. 1D and S-Fig. 2). The functions of NFKBIA in these biological processes are not entirely the same, and it can regulate immune function by participating in various processes such as DDX58/IFIH1 mediated induction of interaction alpha/beta, TAK1 dependent IKK and NF-kB activation, and TCR signaling. It can be seen that a full interpretation of the role and mechanism of NFKBIA in the disease process will help facilitate the diagnosis and treatment of disease. Then the question arises, does NFKBIA play an important role in cancers?

3.2. The expression of NFKBIA in pan-cancer

Given that NFKBIA has such an important biological function, we further explored its potential value in cancers. In order to present

our research results more concisely, we will use more abbreviations for cancers as illustrated in Table 1. First, we tested for differences of NFKBIA expression in pan-cancer using the three databases canSAR (Fig. 2A and S-Table 1), Oncomine (Fig. 2B), and TCGA (Fig. 2C). We determined that the expression of NFKBIA was enhanced to varying degrees in the tumor groups CHOL, ESCA, GBM, HNSC, and KIRC. However, we also note that in the tumor groups BLCA, BRCA, COAD, KICH, LUAD, LUSC, PAAD, PCPG, PRAD, READ, STAD, THCA, and UCEC, the level of expression of NFKBIA showed varying degrees of decrease. At the same time, we also explored the expression of NFKBIA protein in pan-carcinoma through tissue sections (S-Fig. 3). The staining results included in the database show that NFKBIA protein exhibits weak to moderate cytoplasmic positivity in most types of cancer. Hepatocellular carcinoma, as well as some lung cancer, testicular cancer, gastric cancer, and kidney cancer, are all negative. Moreover, the database compared survival analysis data and showed that NFKBIA is closely related to the prognosis of breast cancer, and high expression of NFKBIA is beneficial for the prognosis of patients. Based on the analysis of immunohistochemistry results, we suggest further investigation of the potential role of NFKBIA in BRCA. In view of the significant differences of NFKBIA expression in pan-cancer, we need to further explore its potential function in different cancer types.

3.3. Clinical relevance of NFKBIA

The prognosis of cancer is our most important treatment indicator. Therefore, we will first start with correlations between NFKBIA and cancer prognosis to explore its potential function in pan-cancer. Comprehensive analysis of the prognostic results (Fig. 3A–D and S-Fig. 4) revealed that patients with high expression of NFKBIA in LGG have a better prognosis (OS, DSS, and PFI) using both the KM method and the Cox model, especially within 11 years of treatment. We also have identified that in BRCA, high levels of NFKBIA expression in the first 18 months are beneficial for patient prognosis, whether analyzed from an OS or DSS perspective. We were pleasantly surprised to find that in SARC, high levels of NFKBIA expression throughout the entire follow-up period were shown to be beneficial for patient prognosis in terms of OS and DSS analysis. However, the follow-up period for SARC patients included in the database is only 16 months, which is relatively short. Further follow-up studies are still necessary. A longer follow-up time often indicates the long-term prognosis of the patients. We found that the follow-up time of SKCM patients included in the database was as long as 30 months, and in the first 28 months, high expression levels of NFKBIA were beneficial for the prognosis of patients, according to OS and DSS analysis. Thus, in some specific cancers, especially in LGG, BRCA, SARC and SKCM, the high expression level of NFKBIA may play a role in improving tumor prognosis. We therefore need to take the potential role of NFKBIA into account in pan-cancer, especially the cancers mentioned above, in order to improve the prognosis and outcome of cancer treatment.

Table 1
Abbreviations for 33 cancers in pan-cancer databases.

Abbreviation	Full name
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	Lymphoid Neoplasm 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
LAML	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
PCPG	Pheochromocytoma and Paraganglioma
PRAD	Prostate adenocarcinoma
READ	Rectum adenocarcinoma
SARC	Sarcoma
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
UVM	Uveal Melanoma

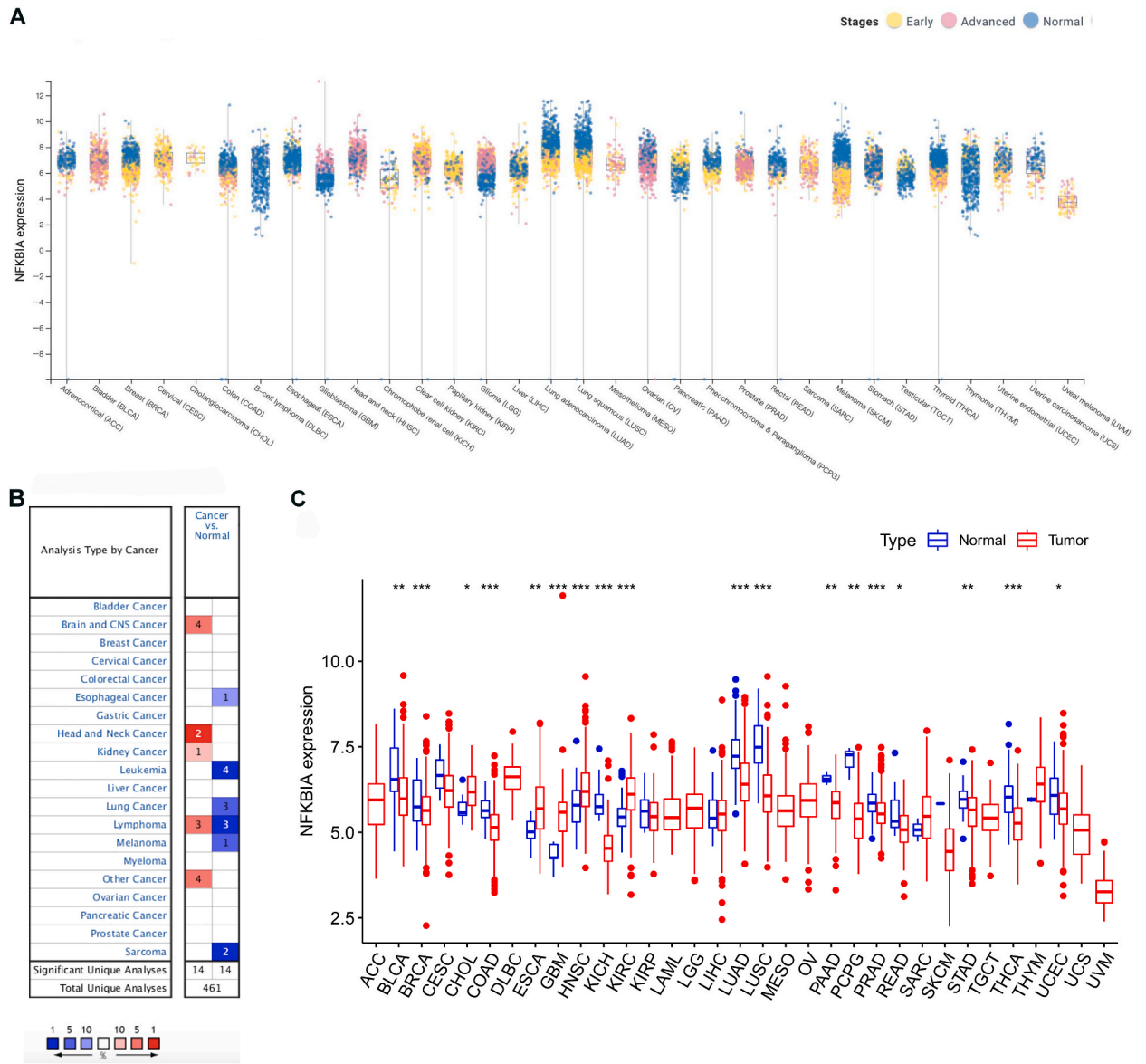

Fig. 2. The expression of NFKBIA in pan-cancer analyzed using the canSAR database (A), the Oncomine database (B) and the TCGA database (C).

NFKBIA is closely related to the prognosis of patients in pan-cancer, but is there any other clinical relevance for NFKBIA? Next, this study explored the potential clinical relevance of NFKBIA through in-depth analysis of pan-cancer data from the TCGA database. We conducted an inductive analysis and found that in HNSC, the expression of NFKBIA was associated with the age of the patient, and the stage and status of the tumor (Fig. 4A–AC). In addition, we also found that in BRCA, DLBC, and THCA, the expression of NFKBIA is related to the age and race of the patients. It can be seen that NFKBIA has extensive clinical relevance in pan-cancer.

3.4. GSEA analysis of NFKBIA in pan-cancer

In order to further explore the role of NFKBIA in pan-cancer, we used GSEA to identify the biological processes in which it participates. Our KEGG analysis showed that in 20 cancers, NFKBIA was enriched in no less than 5 signaling pathways. KEGG analysis further showed that in all 33 cancers, NFKBIA exerts its biological functions through signaling pathways to varying degrees. Surprisingly, NFKBIA was enriched in no less than 5 signaling pathways in 20 cancers (Fig. 5A-T). At the same time, results of GO analysis also showed that NFKBIA performs no less than 5 biological functions in all 33 cancers (S-Fig. 5). We found that NFKBIA is associated with olfactory-transdution in up to 16 types of cancer through statistical analysis of KEGG enrichment. Studies have shown that olfactory receptors can undergo innate and adaptive immune responses during the process of virus entry into the body [29]. Orechioni et al. also found that immune cells, including vascular macrophages, can induce the secretion of interleukin-1β by expressing olfactory

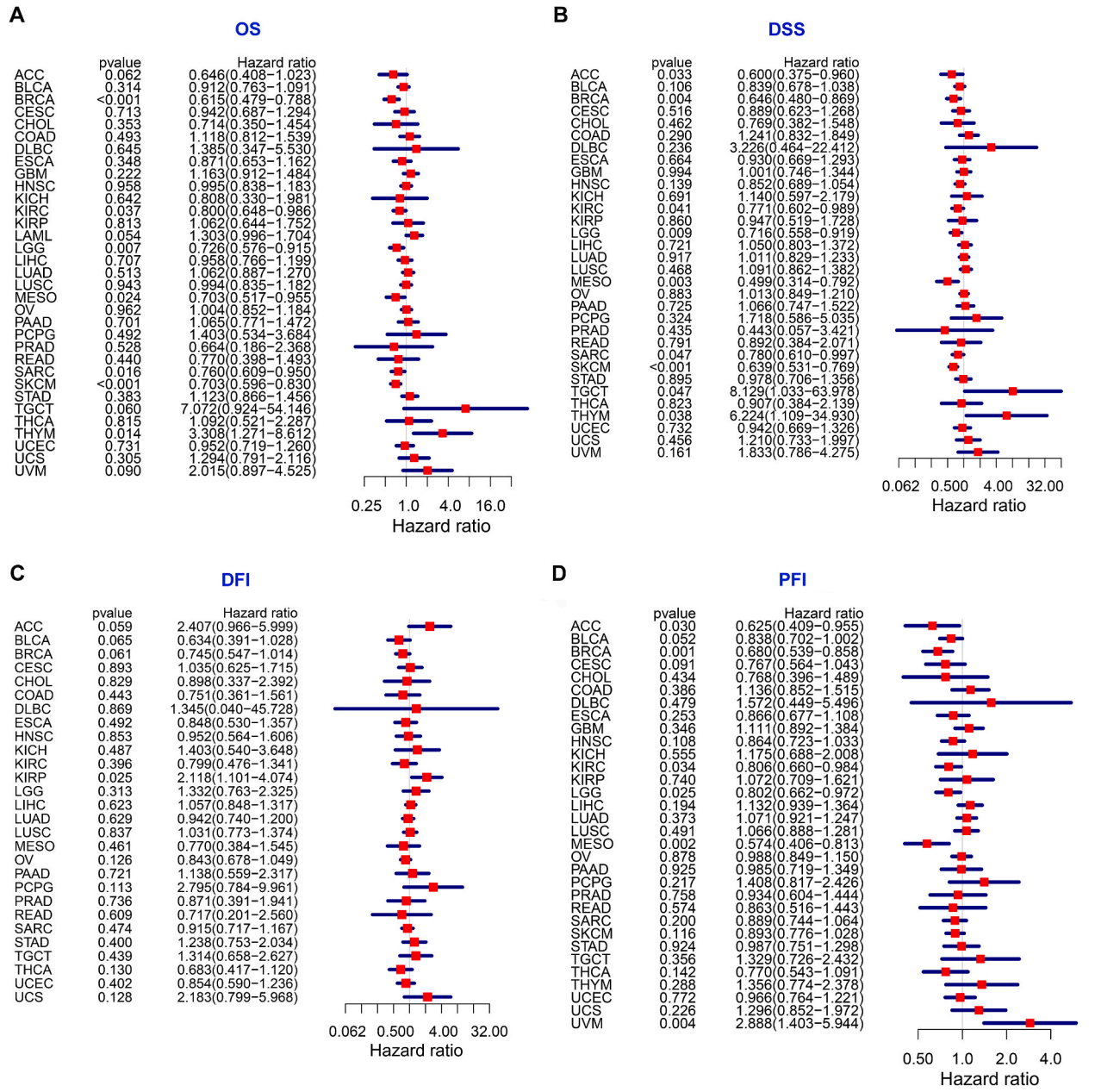

Fig. 3. Cox proportional hazards regression model (Cox model) survival analysis of NFKBIA in pan-cancer, according to overall survival (OS), disease-free interval (DFI), disease-specific survival (DSS) and progression-free interval (PFI).

receptors [30]. It can be seen that the olfactory transduction signaling pathway is involved in tumor immunity. At the same time, our study also found that NFKIBA is enriched in multiple immune related pathways, such as cytokine-cytokine-receptor-interaction, intestinal-immune-network-for-IGA-production, primary-immunodeficiency, T-cell-receptor-signaling-pathway, and B-cell-receptor-signaling-pathway, and so on. In future tumor related research, we may start with NFKBIA and deepen our understanding of tumors through tumor immune related signaling pathways. Thus, NFKBIA participates extensively in the biological processes of pan-cancer in various forms. At the same time, by analyzing the data, we found that NFKBIA is very actively involved in the tumor immune process.

3.5. Analysis of immune-related factors

In order to further explore the potential function of NFKBIA in pan-cancer, we investigated whether NFKBIA is related to the TMB and MSI. We found that there is a significant correlation between NFKBIA and the TMB in BRCA, UVM, UCEC, THYM, THCA, STAD,

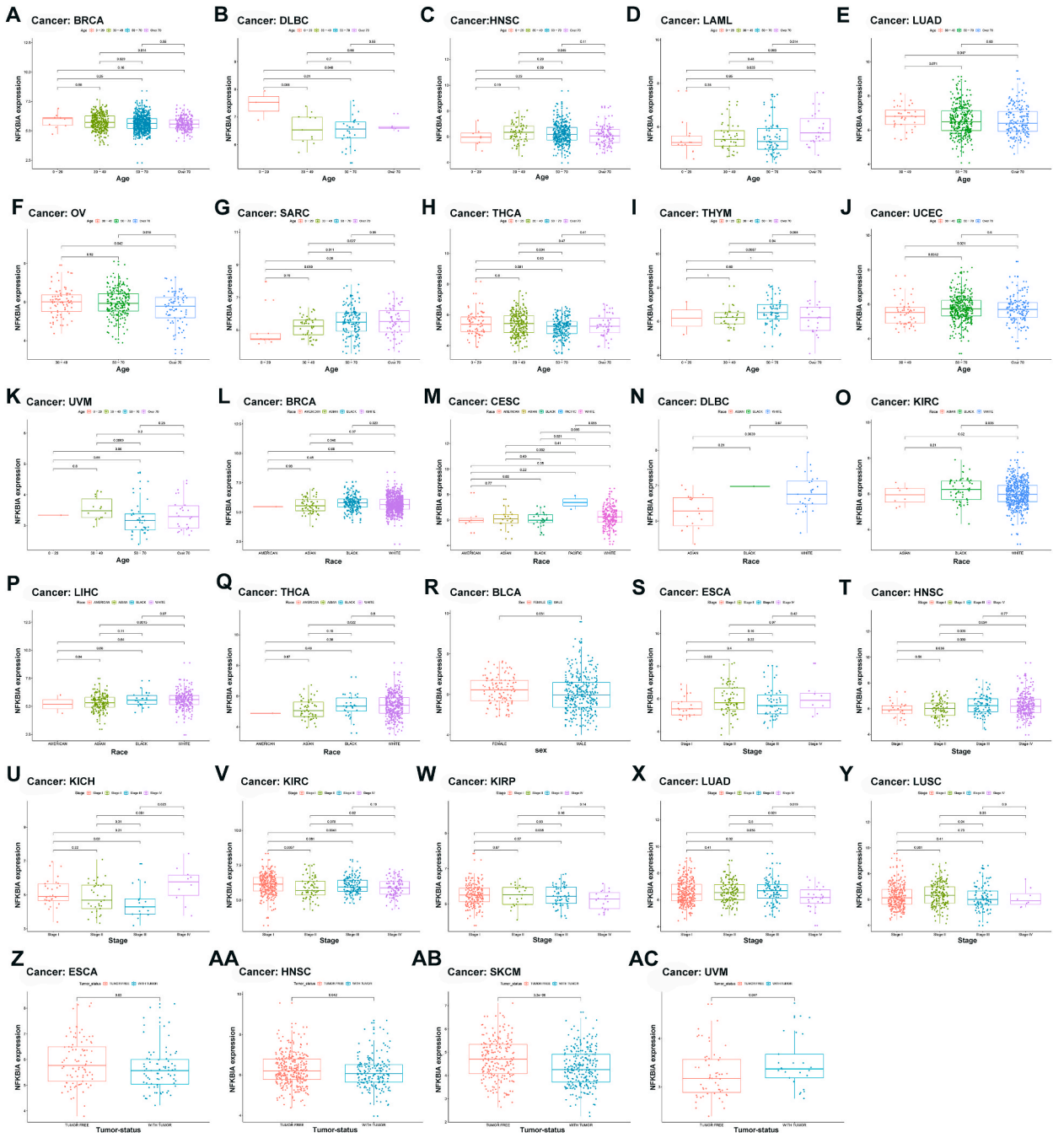

Fig. 4. The clinical relevance of NFKBIA according to the patient's age, race, and tumor stage and status, in the TCGA database data.

LAML, ESCA, and CHOL (Fig. 6A). There is also a significant correlation between NFKBIA and MSI in THCA, STAD, SKCM, READ, PAAD, OV, ESCA, and COAD (Fig. 6B). TMB and MSI are important markers of tumor immunity and its response to treatment, and the results of this correlation analysis show that NFKBIA may play an important role in tumor immunity via this pathway. Because NFKBIA is closely related to the TMB and MSI in pan-cancer, our belief in the value of continuing to explore the role of NFKBIA in pan-cancer was strengthened.

The occurrence and development of tumors is closely related to the patient's immune response status. Therefore, we further explored the potential connection between NFKBIA and tumor immunity in pan-cancer. We first explored whether NFKBIA is related to stromal cells and immune cells, using the TCGA database. This revealed that NFKBIA is correlated with stromal cells or immune cells in 21 cancers (S-Fig. 6 and S-Fig. 7). More surprisingly, NFKBIA was closely associated with both stromal and immune cell levels in up to

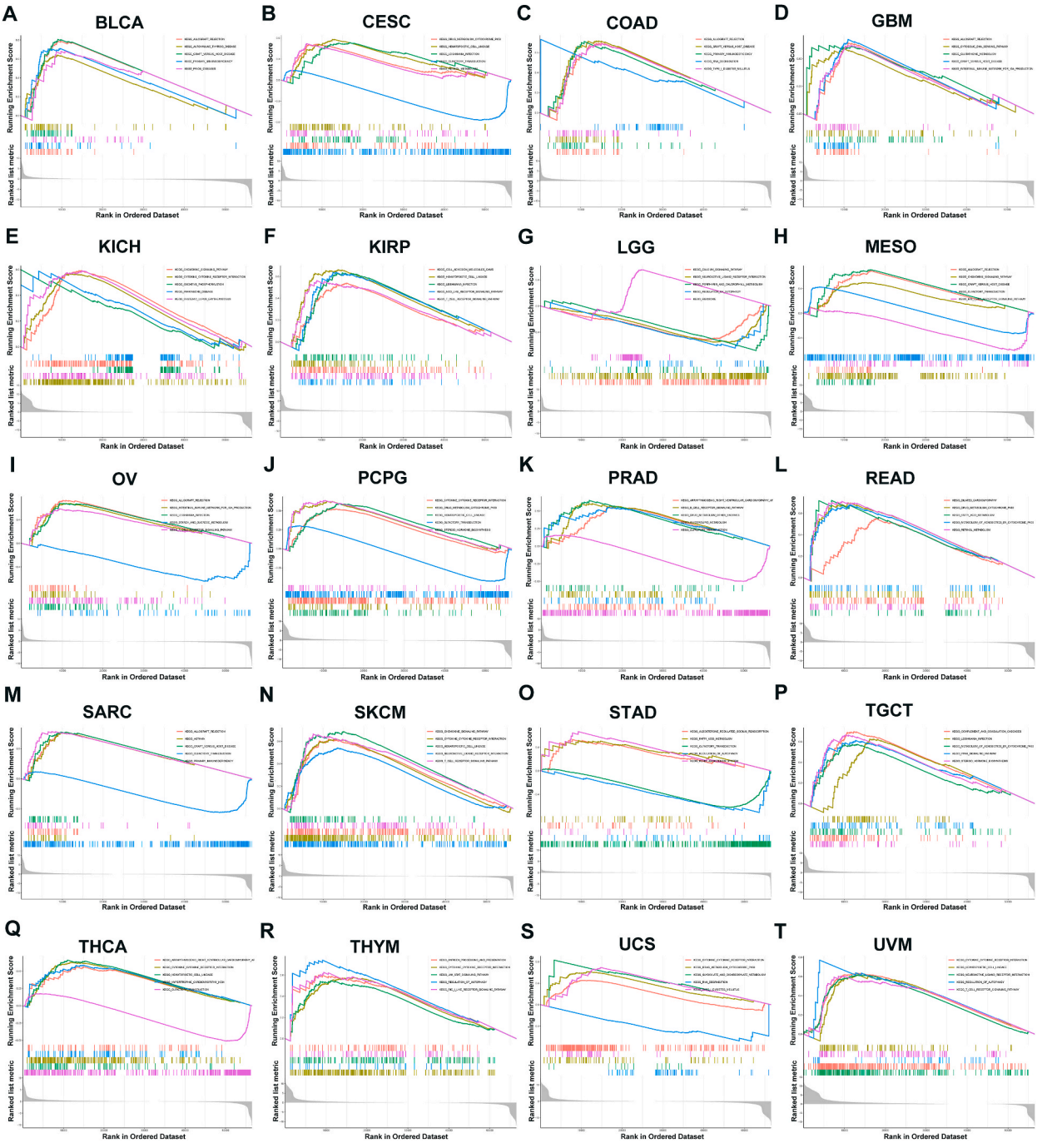

Fig. 5. Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis. In pan-cancer, the KEGG enrichment analysis was performed on NFKBIA using the gene set enrichment analysis (GSEA) database.

12 cancers. We found through comparative analysis of data that NFKBIA is positively correlated with markers of normal cells and immune cells' in SKCM and UVM, and the correlation is more significant. Given that stromal cells and immune cells are important components of the tumor microenvironment and the basis of tumor immune responses, the association of NFKBIA in so many specific cancers further suggested that it may play a critical role in tumor immunity. We particularly recommend further exploring the potential immune response value of NFKBIA in SKCM and UVM.

Next, as NFKBIA is closely related to the level of stromal cells and immune cells in pan-cancer, we further explored the effect of NFKBIA on the infiltration of specific immune cells. After comprehensive analysis, we found that the expression of NFKBIA was related to immune cell infiltration in 8 cancers to varying degrees (S-Fig. 8). Based on the previous analysis of immune value, we suggest

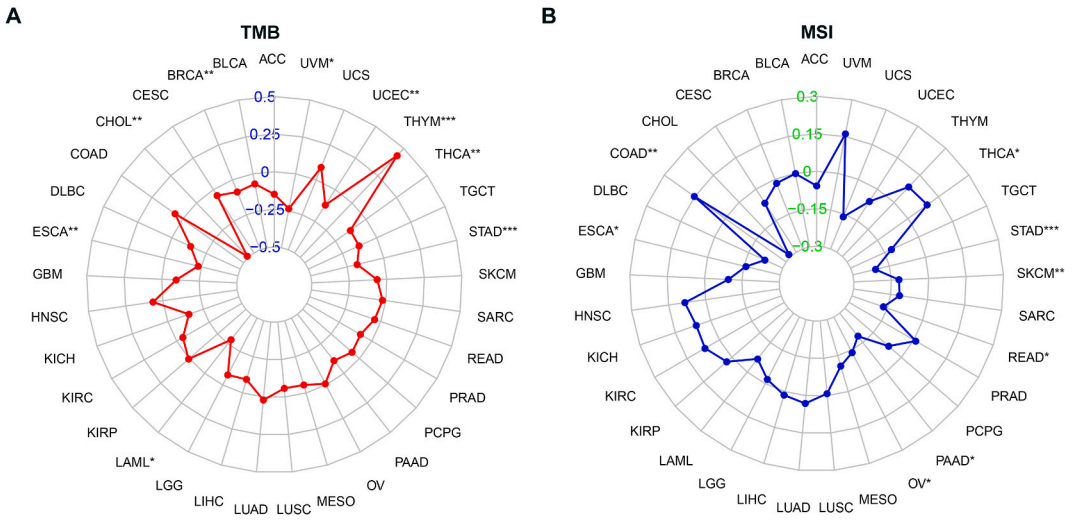

Fig. 6. Microsatellite instability (MSI) and the tumor mutational burden (TMB). The MSI analysis (A) and the TMB analysis (B) of NFKBIA in pan-cancer using the TCGA database.

focusing on exploring the potential association and mechanism between NFKBIA and Macrophages M2 and T cells CD4 memory activated in SKCM. As for UVM, we suggest focusing our research on exploring the potential mechanisms of NFKBIA and T cells CD4 memory activated. This part of the analysis concluded that NFKBIA may change anti-tumor immunity by affecting immune cell infiltration in pan-cancer.

Immunotherapy is an important means of tumor treatment. Immune checkpoints are a type of key factors expressed on immune cells that can regulate the degree of immune activation. They can maintain the activation of the immune system within an appropriate range, effectively resist pathogen invasion, and prevent excessive immune response and the occurrence of autoimmune diseases. The abnormal expression and function of immune checkpoint molecules are one of the important causes of many diseases. Tumor cells can use immune checkpoints to escape the surveillance of the immune system, and thus survive and proliferate [31]. Immune checkpoint inhibitors have been an emerging immunotherapy method in recent years, with significant therapeutic effects in anti-tumor treatment. We attempt to advance immunotherapy by analyzing the potential association between NFKBIA and immune checkpoints. Subsequently, we explored the potential value of NFKBIA for immunotherapy through its influence on immune checkpoint genes in pan-cancer. Surprisingly, we found that in all 33 cancers, NFKBIA had varying degrees of impact on immune checkpoint genes (S-Fig. 9). We found that in PAAD and SKCM, NFKBIA can affect 44 of the 47 immune checkpoint genes. This clearly demonstrates that NFKBIA has a huge potential for immunotherapy.

3.6. ROC analysis of NFKBIA in pan-cancer

Because NFKBIA is widely involved in the pan-cancer disease process, does it have the potential to become a diagnostic marker? To this end, we evaluated the diagnostic value of NFKBIA in pan-cancer through ROC analysis. We present the results of the ROC analysis by area under the curve (AUC), in which the closer the AUC value is to 1, the more likely NFKBIA is to be a potential diagnostic marker in a specific cancer type. We found that in GBM, PAAD, PCPG, and SKCM, the AUC was >0.900 (Fig. 7A–X). Therefore, we speculate that NFKBIA has the potential to become a diagnostic marker in GBM, PAAD, PCPG, and SKCM.

3.7. Potential drugs targeting NFKBIA

In pan-cancer, the function and value of NFKBIA has become increasingly prominent. This study also tried to take NFKBIA as the starting point to explore potential drugs to improve the effect of tumor treatment in order to achieve clinical improvement. We have explored drugs that can target NFKBIA using the DrugBank database, and identify those expected to intervene in the disease process of cancer by targeting NFKBIA. This resulted in the identification of Aspirin, Astaxanthin, and Bardoxolone methyl with the potential to become pan-cancer therapeutics (Fig. 8A–C). Aspirin can be involved in interfering with various cancer signaling pathways, sometimes inducing or up regulating tumor suppressor genes [32,33], and research shows that long-term use of Aspirin can prevent many types of cancer, including pancreatic cancer, gastric cancer, liver cancer, and colorectal cancer [34]. Aspirin has been proven to have an inhibitory effect on NFKBIA. Bardoxolone methyl can inhibit the activity of NF-kB activated by inflammatory factors such as tumor necrosis factor in cancer cells. It plays a role in regulating basic physiological differences in oxidative stress response between cancer cells and non-cancer cells. This drug is toxic to cancer cells, but can induce protective antioxidant and anti-inflammatory responses in normal cells, but it is still in the experimental stage in specific cancer treatments. Due to its ability to mediate antioxidant and anti-inflammatory effects, Astaxanthin may have potential effects on tumor cells. The regulation of NFKBIA by Astaxanthin and its role

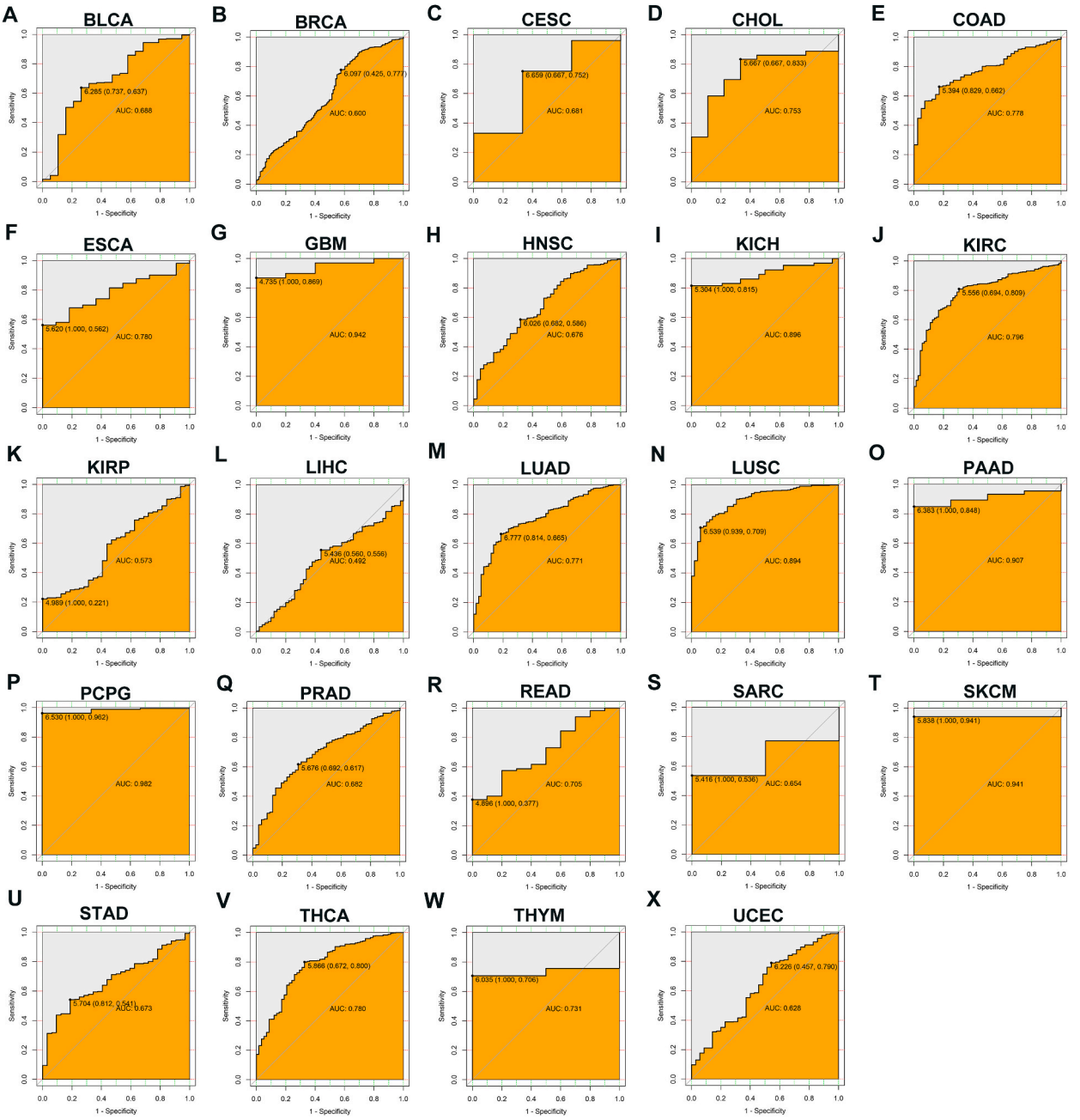

Fig. 7. Receiver operating characteristic (ROC) analysis of NFKBIA. In pan-cancer, the potential diagnostic value of NFKBIA was identified by applying ROC analysis.

in cancer is currently in the research stage. Because the sensitivity of drugs to different bodily environments will fluctuate greatly, we used the COSMIC database to explore drugs that have obvious sensitivity changes regarding the expression of NFKBIA, in order to more effectively treat specific cancers. We found that the sensitivity of Daporinad, Selumetinib, GSK1070916, AICA Ribonucleotide, and MG-132 is closely related to the expression of NFKBIA (Fig. 8D–H), but their potential association with NFKBIA and their role in cancer still need further investigation. The findings of this study may help to guide further pan-cancer research and clinical treatment.

3.8. Gene mutation analysis

Changes in tumor suppressor genes or oncogenes may lead to abnormal signaling pathways, affecting abnormal cell growth, proliferation, differentiation, and cancer metastasis [35]. We analyzed the mutation sites of NFKBIA using the cBioPortal tool and

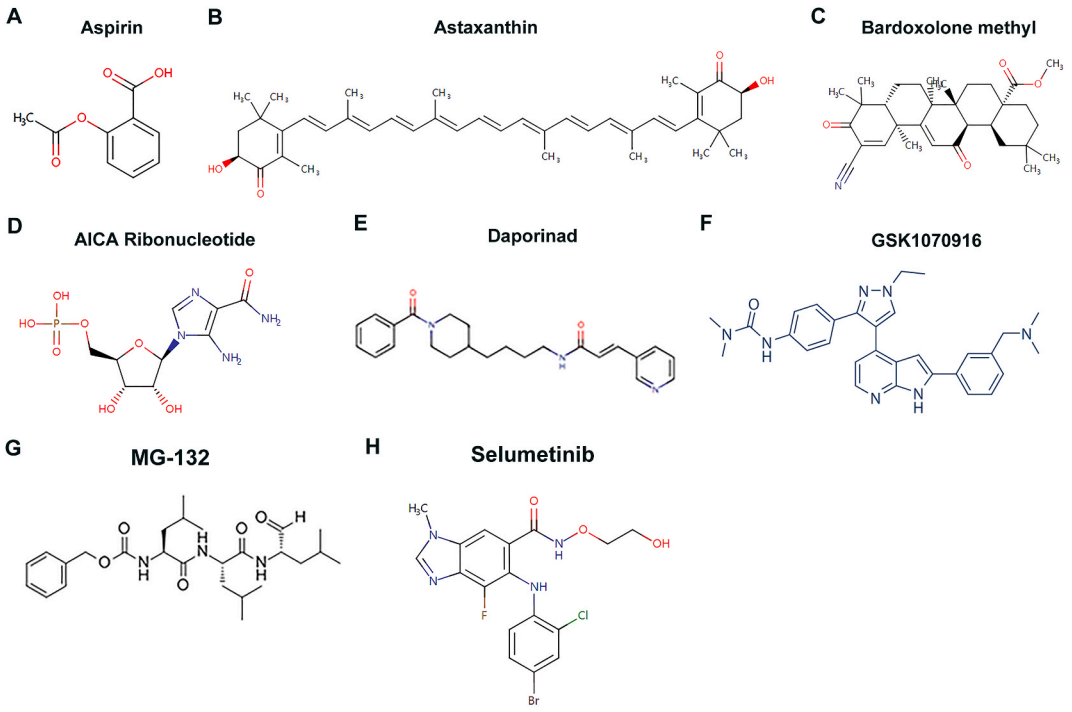

Fig. 8. Identification of drugs related to NFKBIA. Potential drugs targeting NFKBIA in the DrugBank database (A–C). Drugs with altered drug sensitivity related to NFKBIA expression (D–H).

identified "missense" as the main type of genetic change (S-Fig. 10.A). The maximum alteration frequency of NFKBIA in cancers exceeds 10 %, with “amplification” being the main type of genetic change, and “mutation” being the second most important type (S-Fig. 10.B). NFKBIA gene altered in 10.95 % of 566 cases in LUAD and in 8.33 % of 48 cases in DLBC.

4. Discussion

Since the beginning of the 21st century, cancer, with >90 million patients worldwide, remains a prominent public health problem and a major cause of death which seriously threatens to slow the increase in human life expectancy [36,37]. Our research showed that NFKBIA is widely involved in the pathological processes of pan-cancer, and taking NFKBIA as a focus for research will help to deepen the exploration of the pathological mechanisms of cancer.

The expression of NFKBIA in 33 cancers is diverse, which may depend on the different functions of NFKBIA in these different cancers. The study of Kolesnichenko et al. showed that in the human osteosarcoma cell line U-2 OS, the inhibition of NFKBIA can induce the activation of IKK- and p65/RelA to further the process of cell senescence [38]. Lu et al. found that NFKBIA can inhibit the proliferation and invasion of gastric cancer cells [39]. Compared with previous studies, exploring the potential functions of NFKBIA in a single cancer, our research focuses more on the comprehensive analysis of the potential value of NFKBIA in pan-cancers from a more macro perspective, which will help lead the exploration and research in related fields.

The poor prognosis of many cancers can be attributed to delayed diagnosis [40]. Therefore, there is an urgent need to discover new diagnostic biomarkers to achieve early diagnosis of cancer. With its multiple biological functions, NFKBIA is extremely widely involved in basic cancer disease processes. Kinker and Miyar et al. found that in glioma, low expression of NFKBIA often indicates a poor prognosis, and that NFKBIA has the potential to become a diagnostic marker for glioma [41,42]. Our research also suggests that NFKBIA has the potential to become a diagnostic biomarker for GBM. Therefore, we should pay special attention to the diagnostic value of NFKBIA for GBM and further explore it. Meanwhile, based on our analysis results, we should also explore the potential value of NFKBIA as a diagnostic biomarker for PAAD, PCPG, and SKCM. However, this still requires further in vivo and in vitro validation to confirm reliability.

Immunotherapy is one of the greatest advances in the treatment of cancer in recent years. Our research shows that NFKBIA has the potential to become a target for cancer immunotherapy. Through a comprehensive analysis of the results, we found that BRCA patients have low expression of NFKBIA, which is significantly related to the poor prognosis of this cancer. Xiaoyue Shi et al. reached similar conclusions to us and demonstrated through in vitro cell experiments that overexpression of NFKBIA inhibits the proliferation and migration of BRCA cells [43]. Weiwei Yang et al. found through their study of the circadian rhythm of breast tumors that in triple negative breast cancer, NFIL3 can promote cancer progression by inhibiting the transcription of NFKBIA and enhancing the inflammatory response associated with NF-κB signaling pathway [44]. Due to the inhibitory effect of NFKBIA on tumor cell proliferation,

migration, and NF-κB signaling pathway related inflammatory responses in BRCA, NFKBIA is expressed at low levels in BRCA, and its expression level is positively correlated with prognosis.

At the same time, NFKBIA was closely related to the age and race of patients with BRCA. In addition, NFKBIA can affect the levels of TMB, stromal cells and immune cells, immune cell infiltration, and immune checkpoint gene expression in BRCA patients, participate in the immune response by changing the TME to affect the pathological process of BRCA. The TME plays an important role in cross-talk between tumor cells, and in-depth research on improving it provides a new direction for tumor therapy [45,46]. Therefore, in the field of BRCA research, we should focus on exploring the potential value of NFKBIA in cancer prognosis and immunotherapy, so as to improve the short-term and long-term efficacy of BRCA treatment. In recent years, exploring the function of NFKBIA in the course of breast cancer, diagnosis and treatment, has become a focus of attention and our findings strengthen the importance of this area of work. As mentioned earlier, NFKBIA has a significant impact on the prognosis and tumor immunity of BRCA, which will guide experimental and clinical research in related cancer fields in the future.

For the treatment of cancer, we also identified Aspirin, Astaxanthin and Bardoxolone methyl as three drugs with potential therapeutic effects by using NFKBIA as the starting point. As a common non-steroidal anti-inflammatory drug, aspirin is mostly used in the treatment of cardiovascular diseases. In addition, a large number of studies has also shown that aspirin has a potential preventive effect on cancer [47,48]. Aspirin may interfere with the occurrence of tumors by inhibiting COX targets or interfering with COX-independent pathways [49,50]. Astaxanthin, an antioxidant extracted from red aquatic organisms, can inhibit inflammation and apoptosis [51]. In the field of anti-tumor therapy, astaxanthin is often used as an adjuvant chemotherapy drug, as a protective agent to reduce the side effects of chemotherapy drugs [52,53]. Bardoxolone methyl is cytotoxic to tumor cells in prostate cancer, breast cancer, and ovarian cancer, but its toxicity to normal cells is minimal [54,55]. Accumulating studies have shown that Bardoxolone methyl has multiple targets, including NF-kB, JAK/STAT, Wnt/b-catenin, but the molecular mechanism of its anti-cancer effect has not yet been elucidated [56]. In pan-cancer, the three drugs mentioned above all have potential for cancer treatment. However, when used in the treatment of specific cancer, their efficacy still requires verification.

Although this study may have significance for guiding cancer research, there are still some shortcomings. The conclusions of this study are based on bioinformatics analysis and statistical analysis of pan-cancer data in the database, which may lead to deviations in the analysis results, and due to our limited experimental conditions, we have not been able to carry out specific studies to confirm that NFKBIA has a crucial role in pan-cancer.

In summary, this study found that NFKBIA is expressed at different levels in different cancers, which show some correlations with the prognosis, diagnosis, treatment value and clinical and immune status. This may provide guidance for cancer-related research and clinical diagnosis and treatment.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request in compliance with ethical standards.

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CRediT authorship contribution statement

Bin Wang: Writing – original draft, Software, Funding acquisition, Conceptualization. **Difang Sun:** Writing – original draft, Software, Methodology, Funding acquisition, Data curation. **Haifeng Li:** Software. **Jinli Chen:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Bin Wang reports financial support was provided by Qingdao University and Shandong Province Natural Science Foundation. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e31204.

References

[1] F. Bray, et al., Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J Clin 74 (3) (2024) 229–263.
[2] J.A. Schmid, A. Birbach, IkappaB kinase beta (IKKbeta/IKK2/IKBKB)–a key molecule in signaling to the transcription factor NF-kappaB, Cytokine Growth Factor Rev. 19 (2) (2008) 157–165.
[3] Q. Li, I.M. Verma, NF-kappaB regulation in the immune system, Nat. Rev. Immunol. 2 (10) (2002) 725–734.
[4] B. Hoesel, J.A. Schmid, The complexity of NF-κB signaling in inflammation and cancer, Mol. Cancer 12 (2013) 86.
[5] I. Mellman, G. Coukos, G. Dranoff, Cancer immunotherapy comes of age, Nature 480 (7378) (2011) 480–489.
[6] C. Picard, J.L. Casanova, A. Puel, Infectious diseases in patients with IRAK-4, MyD88, NEMO, or IκBα deficiency, Clin. Microbiol. Rev. 24 (3) (2011) 490–497.
[7] K. Taniguchi, M. Karin, NF-κB, inflammation, immunity and cancer: coming of age, Nat. Rev. Immunol. 18 (5) (2018) 309–324.
[8] J.N. Weinstein, et al., The cancer genome Atlas pan-cancer analysis project, Nat. Genet. 45 (10) (2013) 1113–1120.
[9] K.L. Howe, et al., Ensembl 2021, Nucleic Acids Res. 49 (D1) (2021) D884–d891.
[10] F. Pontén, K. Jirström, M. Uhlen, The human protein atlas–a tool for pathology, J. Pathol. 216 (4) (2008) 387–393.
[11] D. Szklarczyk, et al., STRING v11: protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets, Nucleic Acids Res. 47 (D1) (2019) D607–d613.
[12] B. Jassal, et al., The reactome pathway knowledgebase, Nucleic Acids Res. 48 (D1) (2020) D498–d503.
[13] C. Mitsopoulos, et al., canSAR: update to the cancer translational research and drug discovery knowledgebase, Nucleic Acids Res. 49 (D1) (2021) D1074–d1082.
[14] D.R. Rhodes, et al., Oncomine 3.0: genes, pathways, and networks in a collection of 18,000 cancer gene expression profiles, Neoplasia 9 (2) (2007) 166–180.
[15] Y. Chen, et al., Pan-cancer analysis reveals an immunological role and prognostic potential of PXN in human cancer, Aging (Albany NY) 13 (12) (2021) 16248–16266.
[16] H.X. Wu, et al., Tumor mutational and indel burden: a systematic pan-cancer evaluation as prognostic biomarkers, Ann. Transl. Med. 7 (22) (2019) 640.
[17] W.H. Chang, A.G. Lai, Aberrations in Notch-Hedgehog signalling reveal cancer stem cells harbouring conserved oncogenic properties associated with hypoxia and immunoevasion, Br. J. Cancer 121 (8) (2019) 666–678.
[18] M.G. McNamara, et al., Impact of high tumor mutational burden in solid tumors and challenges for biomarker application, Cancer Treat Rev. 89 (2020) 102084.
[19] T. Liu, M. Zhang, D. Sun, Immune cell infiltration and identifying genes of prognostic value in the papillary renal cell carcinoma microenvironment by bioinformatics analysis, BioMed Res. Int. 2020 (2020) 5019746.
[20] D.S. Chen, I. Mellman, Elements of cancer immunity and the cancer-immune set point, Nature 541 (7637) (2017) 321–330.
[21] A. Batista, et al., IRE1α regulates macrophage polarization, PD-L1 expression, and tumor survival, PLoS Biol. 18 (6) (2020) e3000687.
[22] L. Xu, Y. Jin, X. Qin, Comprehensive analysis of significant genes and immune cell infiltration in HPV-related head and neck squamous cell carcinoma, Int. Immunopharm. 87 (2020) 106844.
[23] J.A. Seidel, A. Otsuka, K. Kabashima, Anti-PD-1 and anti-CTLA-4 therapies in cancer: mechanisms of action, efficacy, and limitations, Front. Oncol. 8 (2018) 86.
[24] A. Subramanian, et al., Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles, Proc. Natl. Acad. Sci. U. S. A. 102 (43) (2005) 15545–15550.
[25] X. Robin, et al., pROC: an open-source package for R and S+ to analyze and compare ROC curves, BMC Bioinf. 12 (2011) 77.
[26] D.S. Wishart, et al., DrugBank 5.0: a major update to the DrugBank database for 2018, Nucleic Acids Res. 46 (D1) (2018) D1074–d1082.
[27] J.G. Tate, et al., COSMIC: the catalogue of somatic mutations in cancer, Nucleic Acids Res. 47 (D1) (2019) D941–d947.
[28] J. Gao, et al., Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal, Sci. Signal. 6 (269) (2013) pl1.
[29] D.M. Durrant, S. Ghosh, R.S. Klein, The olfactory bulb: an immunosensory effector organ during neurotropic viral infections, ACS Chem. Neurosci. 7 (4) (2016) 464–469.
[30] M. Orecchioni, et al., Olfactory receptor 2 in vascular macrophages drives atherosclerosis by NLRP3-dependent IL-1 production, Science 375 (6577) (2022) 214–221.
[31] G. Elia, et al., New insight in endocrine-related adverse events associated to immune checkpoint blockade, Best Pract. Res. Clin. Endocrinol. Metabol. 34 (1) (2020) 101370.
[32] L. Alfonso, et al., Molecular targets of aspirin and cancer prevention, Br. J. Cancer 111 (1) (2014) 61–67.
[33] D. Li, et al., Tumor-preventing activity of aspirin in multiple cancers based on bioinformatic analyses, PeerJ 6 (2018) e5667.
[34] H. Arif, S. Aggarwal, Salicylic acid (aspirin), in StatPearls, in: StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC., Treasure Island (FL), 2024.
[35] B.P. Kopnin, Targets of oncogenes and tumor suppressors: key for understanding basic mechanisms of carcinogenesis, Biochemistry (Mosc). 65 (1) (2000) 2–27.
[36] F. Bray, et al., Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J Clin 68 (6) (2018) 394–424.
[37] Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015, Lancet 388 (10053) (2016) 1545–1602.
[38] M. Kolesnichenko, et al., Transcriptional repression of NFKBIA triggers constitutive IKK- and proteasome-independent p65/RelA activation in senescence, EMBO J. 40 (6) (2021) e104296.
[39] J. Lu, et al., circ-CEP85L suppresses the proliferation and invasion of gastric cancer by regulating NFKBIA expression via miR-942-5p, J. Cell. Physiol. 235 (9) (2020) 6287–6299.
[40] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, CA Cancer J Clin. 69 (1) (2019) 7–34, 2019.
[41] G.S. Kinker, et al., Deletion and low expression of NFKBIA are associated with poor prognosis in lower-grade glioma patients, Sci. Rep. 6 (2016) 24160.
[42] A. Miyar, et al., Predictive and prognostic value of TLR9 and NFKBIA gene expression as potential biomarkers for human glioma diagnosis, J. Neurol. Sci. 368 (2016) 314–317.
[43] X. Shi, et al., Comprehensive evaluation of cell death-related genes as novel diagnostic biomarkers for breast cancer, Heliyon 9 (11) (2023) e21341.
[44] W. Yang, et al., Elevated expression of the rhythm gene NFIL3 promotes the progression of TNBC by activating NF-κB signaling through suppression of NFKBIA transcription, J. Exp. Clin. Cancer Res. 41 (1) (2022) 67.
[45] C. Solinas, et al., The immune infiltrate in prostate, bladder and testicular tumors: an old friend for new challenges, Cancer Treat Rev. 53 (2017) 138–145.
[46] C. Solinas, et al., Tumor-infiltrating lymphocytes in breast cancer according to tumor subtype: current state of the art, Breast 35 (2017) 142–150.
[47] Y. Song, et al., Aspirin and its potential preventive role in cancer: an umbrella review, Front. Endocrinol. 11 (2020) 3.
[48] D. Capodanno, D.J. Angiolillo, Aspirin for primary cardiovascular risk prevention and beyond in diabetes mellitus, Circulation 134 (20) (2016) 1579–1594.
[49] N. Nath, et al., Nitro-aspirin inhibits MCF-7 breast cancer cell growth: effects on COX-2 expression and Wnt/beta-catenin/TCF-4 signaling, Biochem. Pharmacol. 78 (10) (2009) 1298–1304.
[50] G. Pozzoli, et al., Aspirin inhibits proliferation and promotes differentiation of neuroblastoma cells via p21(Waf1) protein up-regulation and Rb1 pathway modulation, J. Cell Mol. Med. 23 (10) (2019) 7078–7087.
[51] H. Wu, et al., Astaxanthin as a potential neuroprotective agent for neurological diseases, Mar. Drugs 13 (9) (2015) 5750–5766.
[52] K. Kavitha, et al., Astaxanthin inhibits NF-κB and Wnt/β-catenin signaling pathways via inactivation of Erk/MAPK and PI3K/Akt to induce intrinsic apoptosis in a hamster model of oral cancer, Biochim. Biophys. Acta 1830 (10) (2013) 4433–4444.
[53] T. Ozben, Antioxidant supplementation on cancer risk and concurrent use of antioxidants during cancer therapy: an update, Curr. Top. Med. Chem. 15 (2) (2014) 170–178.

[54] X.Y. Wang, et al., Bardoxolone methyl (CDDO-Me or RTA402) induces cell cycle arrest, apoptosis and autophagy via PI3K/Akt/mTOR and p38 MAPK/Erk1/2 signaling pathways in K562 cells, Am J Transl Res 9 (10) (2017) 4652–4672.
[55] Y.Y. Wang, H. Zhe, R. Zhao, Preclinical evidences toward the use of triterpenoid CDDO-Me for solid cancer prevention and treatment, Mol. Cancer 13 (2014) 30.
[56] L. Zhou, et al., CDDO-me elicits anti-breast cancer activity by targeting LRP6 and FZD7 receptor complex, J. Pharmacol. Exp. Therapeut. 373 (1) (2020) 149–159.