Comprehensive Analysis of Immune Correlation of KIF20A in Pan-cancer

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Abstract

Background: Cancer is one of the most common causes of death, and the morbidity and mortality are gradually increasing in the world. KIF20A plays an important role in tumors, but its immune relevance in pan-cancer needs to be further studied.

Methods: KIF20A-related information was download from The Cancer Genome Atlas (TCGA). Collecting RNA-seq data is fragments per kilobase million (FPKM) style data. The ESTIMATE algorithm was used for estimating the stromal and immune scores for 33 tumors. Then, we analyzed the correlation between KIF20A in pan-cancer and immune checkpoints and performed gene set enrichment analysis (GSEA) analysis on the co-expressed genes of KIF20A in pan-cancer.

Results: We have confirmed that the expression of KIF20A has a intensive correlation with prognosis in 33 kinds of tumors. Its expression of KIF20A was related to a variety of immune cells and immune checkpoints. Based on the results of GSEA for further analysis, in multiple tumors, KIF20A is related to immune-related pathways.

Conclusion: We have demonstrated that KIF20A played an important role in pan-cancer and could affect the occurrence or development of a variety of tumors. Moreover, KIF20A was related to immunity, and KIF20A- related immune research in pan-cancer also needs to be further demonstrate.

1. Introduction

As a deadly disease that has plagued mankind for centuries, cancer is gradually being one of the most common causes of death worldwide, and its morbidity and mortality are still growing rapidly year by year (1). It is estimated that in 2018 there were more than 18.1 million new cancer cases and more than 9.6 million cancer-related deaths all over the world (1, 2). Up to now, early diagnosis and treatment is still the most effective way to enhance the prognosis and even cure the patients of many cancers. However, for advanced or terminal-stage patients, multiple therapy including molecular targeted therapy or immunotherapy have not yielded an encouraging result (3). Therefore, the discovery of effective biomarkers that could diagnose and treat tumors in early stage will effectively improve the prognosis of patients.

Kinesins participate in meiosis, mitosis, and intracellular vesicle transport in various cells(4, 5). As a member of kinesin, kinesin family member 20A (KIF20A), which is also known as Rab6-binding kinesin (RAB6KIFL) and mitotic kinesin-like protein 2 (MKLP2), located on chromosome 5q31.2 (6–8). In fact, there are few studies related to KIF20A, but it has been confirmed that KIF20A is associated to the occurrence and development of multiple tumors. For example, Imai and their colleagues used HLA-A2 transgenic mice (Tgm) to identify human KIF20A-derived and HLA-A2-restricted cytotoxic T lymphocyte (CTL) epitopes, further confirming the effectiveness and safety of KIF20A reactive CTL for killing tumor cells (9). Another aspect, Zhang and their colleagues revealed that KIF20A may play a crucial role in the proliferation, migration and invasion of colorectal cancer (10). Moreover, Shen and their colleagues

demonstrated that KIF20A could promotes the proliferation and metastasis of bladder cancer cells (11). Zhang and their colleagues explored that KIF20A could reduce proliferation, migration, and invasion in prostate cancer cell lines (12).

In this study, based on the TCGA data downloaded from UCSC Xena, we conducted a series of bioinformatics analysis to explore the role of KIF20A in 33 tumors. Kaplan-Meier survival curves and clinical correlation analysis were conducted to analysis the prognosis effect of KIF20A. Tumor mutational burden (TMB) and microenvironment stability(MSI)were also calculated to detect the potential role of KIF20A in tumors. Then, a co-expressed analysis was conducted between KIF20A and immune checkpoint genes to verify the immune correlation of KIF20A. Last, gene set enrichment analysis (GSEA) was utilized to explore the biological functions of KIF20A in pan-cancer.

2. Materials And Methods

2.1 Data acquisition

The RNA-sequence data of KIF20A expression in multiple cancers and corresponding normal tissues stored in TCGA were obtained through the UCSC (University of California, Santa Cruz) Xena database (<https://xenabrowser.net/>), an open-access resource integrating the genomic and clinical information of 33 cancers in TCGA. Collected RNA-seq data is fragments per kilobase million (FPKM) style data. The clinical and survival information of TCGA patients was downloaded in the form of “bcr xml” file.

2.2 Clinical correlation and prognosis analysis

All the patients were divided into those with high KIF20A expression and those with low KIF20A expression based on the gene expression profile data. Kaplan-Meier survival curves were used for compared the prognosis difference between high and low KIF20A expression group (Overall survival, OS; Disease-specific survival, DSS; Disease-free interval, DFI; Progression-free interval, PFI). Moreover, the information of the clinical stage was also used for analyzing the clinical difference between these two groups. The significant threshold was all set as $P < 0.05$.

2.3 The analysis of tumor mutation burden, microsatellite instability and tumor microenvironment with KIF20A

The TMB score of samples in 33 tumors was calculated using author’s own perl code. Spearman analysis was used to determine the correlation between KIF20A and TMB in pan-cancer. The data of microsatellite instability were downloaded from TCGA in the form of “bam” file. Meanwhile, the correlation between KIF20A and MSI was analyzed. The ESTIMATE package was used for calculated the stromal and immune scores for 33 tumors.

2.4 Genes Co-expressed with KIF20A in Pan-Cancer

The correlation between 47 immune-related genes and KIF20A were analyzed in 33 tumors under the screening conditions of co-expression interval – 0.5–0.7 and $P < 0.05$. The co-expression result was shown in a heatmap.

2.5 Gene Set Enrichment Analysis

GSEA v4.0.1 was applied to perform GO analysis to investigate the biological functions of KIF20A in 33 tumors. The cutoff value was $FDR < 0.25$ and $NOM\ P\text{-value} < 0.05$.

2.6 Quantitative RT-PCR

Total RNA was freshly prepared utilizing the Total RNA Kit (Omega Bio-tek, Doraville, USA). To get cDNAs, the total RNA was reverse-transcribed. Then, quantitatively RT-PCR was conducted by ABI PRISM 7900 Sequence Detection System (Applied Biosystems, Carlsbad, USA) and SYBR-green-based method. Next, the Ct value (cycle number at threshold) was utilized to compute the relative amount of mRNA. To obtain the ΔCt value, the Ct value of each sample was normalized by control GAPDH RNA. Last, the relative mRNA level was got as $2^{-\Delta Ct}$. The primer sets were listed in Table S1.

3. Results

3.1 KIF20A mRNA levels and clinical pathological features have significantly difference in human pan-cancer and the corresponding normal Tissues

The difference of KIF20A expression in 33 tumor tissues and adjacent was compared in by R software, and found highly expressed in most kinds of tumors (Fig. 1A). To further confirm the results of Fig. 1A in the real world, we extracted 20 tumors and matched normal tissues from the three tumors with the highest incidence, lung squamous cell carcinoma (LUSC), breast cancer (BRCA) and colon adenocarcinoma (COAD), respectively. The level of KIF20A mRNA in these tissues was quantified by qRT-PCR and shown in Fig. 1B. The results of prognosis analysis showed that in many tumors, the patients with high expression of KIF20A were associated with poor OS, DSS, DFI and PFI (Fig. 2–5). Last, the trend of the expression of KIF20A in different clinical stages in different tumors was explored, and the expression of KIF20A in a variety of tumors gradually increased as the stage increased, such as adrenocortical carcinoma (ACC), lung adenocarcinoma (LUAD), and kidney renal papillary cell carcinoma (KIRP) (Fig. 6).

3.2 KIF20A-related tumor mutation burden and microsatellite instability analysis

The radar chart showed that the TMB of a variety of tumors was positively correlated with KIF20A, including: ACC, Uterine Carcinosarcoma (UCS), Uterine Corpus Endometrial Carcinoma (UCEC), Testicular Germ Cell Tumors (TGCT), Stomach adenocarcinoma (STAD), Skin Cutaneous Melanoma (SKCM),

Sarcoma (SARC), Rectum adenocarcinoma (READ), Prostate adenocarcinoma (PRAD), Pancreatic adenocarcinoma (PAAD), Mesothelioma (MESO), LUSC, LUAD, Brain Lower Grade Glioma (LGG), Kidney renal clear cell carcinoma (KIRC), Kidney Chromophobe (KICH), COAD, Cholangiocarcinoma (CHOL), BRCA, and Bladder Urothelial Carcinoma (BLCA). Furthermore, the TMB of Thyroid carcinoma (THCA) was negatively correlated with KIF20A expression (Fig. 7). For MSI score, the positive association with KIF20A were found in many cancers, like ACC, UVM, UCEC, STAD, SARC, MESO, LUSC, LIHC, COAD, and Cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), contrast to Lymphoid Neoplasm Diffuse Large B-cell Lymphoma (DLBC) (Fig. 8).

3.3 Analysis of KIF20A-related tumor microenvironment in pan-cancer

The expression level of KIF20A was positively correlated with stromal score in three tumors- KIRC, LGG and THCA. Conversely, the expression level of KIF20A correlated inversely with stromal score in multiple tumors, including BLCA, BRCA, COAD, Glioblastoma multiforme (GBM), LIHC, LUAD, LUSC, SARC, STAD, TGCT, THYM and UCEC (Fig. 9A). Same to stromal score, the expression level of KIF20A was also found positively associated with immune score in KIRC, LGG and THCA (Fig. 9B). In contrast, immune score increased with the mRNA expression of KIF20A increased in GBM, LUSC, SARC, STAD and UCEC. (Fig. 9B).

3.4 Analysis of KIF20A-related immune cell infiltration in pan-cancer

The immune infiltration analysis demonstrated that tKIF20A was related to the immune score (Fig. 9B). Among the KIF20A-related results, the increasing of the proportion of immune cell infiltration was associated with the up-regulation or down-regulation of KIF20A in a variety of tumors, respectively (Fig. 10A-R). Specifically, in the LUSC-related analysis, the up-regulation of KIF20A was positively correlated with the infiltration of macrophages M0, macrophages M1 and NK cells activated (Fig. 10A, B, L). On the contrary, upregulated KIF20A was negatively correlated with the infiltration of mast cells resting (Fig. 10R). In BRCA-related immune infiltrating cells, the increasing of KIF20A was associated with macrophages M0, macrophages M1, T cells follicular helper, T cells CD4 memory activated, and dendritic cells activated (Fig. 10A, B, D, E, M). The decline of KIF20A was related to macrophages M2, mast cells resting and monocytes (Fig. 10C, L, P). KIF20A had a small correlation with immune cell infiltration in COAD, and its increase was related to the dendritic cells activated (Fig. 10M). On the contrary, the decrease of KIF20A was related to the dendritic cells resting (Fig. 10N).

3.5 Co-expression analysis between KIF20A and immune checkpoint gene in pan-cancer

The co-expression relationship between 47 immune checkpoints and KIF20A expression were explored in 33 tumors (Fig. 11). In LUSC, the expression of KIF20A was associated with a variety of immune checkpoint genes, including: CD44, CD86, CD40, TNFRSF4, VRIR, CD27, HHLA2, PDCD1LG2, TNFSF14,

CD80, HAVCR2, CD200R1, CD28, CD48, CTLA4, CD20LG, ICOS, TNFSF4, LAIR1, NRP1, CD200, BTLA. The expression of KIF20A, in BRCA, was related to a large number of immune checkpoint genes, such as: TNFRSF9, CD44, CD86, CD274, TIGIT, TNFSF15, TNFRSF18, VSIR, TNFRSF8, TNFSF9, CD70, PDCD1LG2, IDO1, VTCN1, ICOSLG, IDO2, TNFSF14, LGALS9, PDCD1, CD80, KIR3DL1, CD276, ADORA2A, HAVCR2, CTLA4, ICOS, LAG3, NRP1, TNFRSF14 and CD200. KIF20A was associated with a small number of immune checkpoint genes in COAD, including CD44, TNFSF15, TNFRSF4, VSIP, CD27, TNFSF18, IDO1, IDO2, TNFSF14, CD160, ADORA2A, CD200R1, CD28, CD40LG, LAG3, TNFSF4 and BTLA.

3.6 GSEA analysis of KIF20 in pan-cancer

To better explore the function of KIF20A in different tumors, the GSEA software was utilized to perform GO enrichment of KIF20A. In great part of tumors, KIF20A was associated with the up-regulation of multiple pathways, while in several tumors, KIF20A was associated with the down-regulation of multiple pathways (Fig. 12). In LUSC, KIF20A-related pathways were down-regulated olfactory receptor activity, RNA binding involved in posttranscriptional gene silence, gene silencing by RNA, gene silencing and mRNA binding. KIF20A enriched several up-regulated pathways in BRCA, including chromosome segregation, chromosomal region, olfactory receptor activity, organelle fission and sensory perception of smell. Further, in COAD, we explored the most significant pathways involved in KIF20A, such as positive regulation of G1 s transition of mitotic cell c, positive regulation of cell cycle phase transition, positive regulation of cell cycle G1 s phase transition, olfactory receptor activity, and odorant binging.

4. Discussion

The burden of cancer, which is one of the most critical public health problems globally, is deteriorating at an alarming rate due to aging, the rapid growth of population and the increasing of carcinogenic factors (13). The continuous advancement of high-throughput sequencing in recent years makes it possible for researchers yield insights into the mechanism of tumor initiation and progression (14, 15). So far, the top three malignant tumors with high incidence are lung cancer (1.82 million), breast cancer (1.67 million), and colorectal cancer (1.36 million) (16). It is also worth noting that the malignant tumors with the highest number of deaths are lung cancer (1.6 million deaths), liver cancer (745,000 deaths), and stomach cancer (723,000 deaths) (16). Metastasis and recurrence are the two vital factors leading to the death of tumor patients. For example, the patients with (ER-/PR-/HER2-) are known as the worst prognosis compared with other pathological type(17). Meanwhile, it also has the highest recurrence rate than other types of breast cancer (17). In detail, the five-year specific survival rate for stage I triple-negative breast cancer is 85%, significantly lower that the 94% – 99% survival rate of hormone receptor positive and ERBB2 positive patients(17). The median OS of metastatic triple-negative breast cancer is about one year, while other two subtypes is about five years. Therefore, it is crucial to find effective prevention strategies, diagnostic methods and treatment ways to improve the OS of patients with malignant tumors. The research on the molecular mechanism of tumorigenesis is helpful to discover new biomarkers.

Recently, with the significant breakthrough obtained in tumor immunotherapy, immunotherapy has become an established treatment for cancers (18). Recently, the U.S. Food and Drug Administration (FDA) has approved MSI as a genetic testing method as a basis for choosing immunotherapy for COAD patients (19). MSI status could be used as a universal biomarker to predict the responsiveness of immunotherapy (19). Considering the fact that the high density of tumor-infiltrating lymphocytes (TILs) was often observed in cancers with high microsatellite instability (MSI-H), it is essential to detect microsatellite instability before immunotherapy (20). TMB is a potential biomarker for predicting the effects immune checkpoint therapy and patient prognosis. Therefore, comprehensive analysis of TMB in tumors and MSI would help determine the potential of KIF20A in pan-cancer immunotherapy.

The discovery of new immune checkpoints is significant in promoting tumor immunotherapy. Among the immune-related genes co-expressed with KIF20A, many genes are closely related to immune cells. For example, Bartkowiak and their colleagues found that TNFRSF9 that expressed on both T cells and antigen-presenting cells, could enhance the effect of activated T cells, further increasing of cytokines and TIL expansion (21). Klement et al. detected that immune checkpoint CD44 could activate multiple cell signaling pathways, thereby a series cell activity inducing cell proliferation, cell survival, cytoskeletal changes and cell motility (22). The results of another study revealed that CD73, CD86, and CD304 are overexpressed in most BCP-ALL patients, and their expression levels remain stable during the whole treatment period. (23).

In fact, KIF20A is enriched in multiple pathways in pan-cancer, and we took several types of tumors with higher incidence for further discussion. Changes in the number and structure of chromosomes are generally considered related to the occurrence of cancer cells (24). This performance in cells is called chromosome instability, which may be caused by the mechanism of chromosome separation. Stefano and their colleagues stated that chromosome separation may lead to genome instability and eventually lead to cell cycle arrest (24). Meanwhile, the changes in the cell cycle and the appearance of aging characteristics were also found resulting in pro-inflammatory signals, thereby promoting its clearance by the immune system (24). Michael and their colleagues demonstrated that ZFP36 RNA-binding protein (RBP) could regulate early T cell activation by down-regulating the expression of activation markers, limiting T cell proliferation and promoting cell apoptosis (25). The CLOCK/BMAL1 complex mediates the stabilization of the cell cycle at the G2/M level by regulating the expression of cyclin B1 in cell cycle regulation (31). CLOCK-BMAL1 complex, a key biomarker for the maintenance and immunosuppression of glioma stem cells, also be verified the correlation between CLOCK-BMAL1 and immunity (26). The immune correlation of breast cancer, colon cancer and lung cancer in our analysis was consistent to the results mentioned above.

There are several limitations to this study. First of all, we did not carry out the functional experimental verification of pan-cancer. Second, the study of KIF20A in pan-cancer should be extensively linked at the pathway level. Third, we provide a lot of evidence to prove the correlation between KIF20A and immunity. However, the specific role of KIF20A on TME and immune cells needs more evidence. Fourth, single genes, that related to the occurrence and development of multiple tumors, are often linked to epigenetics

and metabolism. The interaction between epigenetics, metabolomics and immunity maybe establish a significant network to comprehensive KIF20A in pan-cancer. In conclusion, KIF20A plays an important role in pan-cancer and could affect the occurrence or development of a variety of tumors. KIF20A plays the role of oncogene in most cancers and has the potential to become a biomarker. In addition, KIF20A provides a direction for subsequent tumor immunity research.

Declarations

Ethics approval and consent to participate

This study was approved by the Academic Committee of Changzhou Second People's Hospital affiliated with Nanjing Medical University and was conducted in accordance with the principles expressed in the Helsinki Declaration. All datasets were obtained from published literature, so it can be confirmed that written informed consent was obtained.

Consent to publish

Not applicable.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

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Authors' Contributions

QXH and CFZ designed the study. XHC, RZL, GP and QJP collected the data. XHC, BZ, XDZ, and ZZ performed the data analyses and produced the initial draft of the manuscript. XHC obtained and validated the results. All authors read and approved the final manuscript.

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Figures

Figure 1

The expression levels of KIF20A. Figure 1A: The expression levels of KIF20A between 33 kinds of tumors and normal tissue, respectively. Figure 1B: The expression levels of KIF20A in LUSC, BRCA, and COAD, respectively. (*P-value $\leq$ 0.05, ** P-value $\leq$ 0.01, ***P-value $\leq$ 0.001)

Figure 2

The OS analysis of KIF20A in pan-cancer. The forest plot shows the expression level of KIF20A in 33 tumors and its correlation with OS, respectively. (P-value $\leq$ 0.05)

Figure 3

The DSS analysis of KIF20A in pan-cancer. The forest plot shows the expression level of KIF20A in 33 tumors and its correlation with DSS, respectively. (P-value $\geq$ 0.05)

Figure 4

The DFI analysis of KIF20A in pan-cancer. The forest plot shows the expression level of KIF20A in 33 tumors and its correlation with DFI, respectively. (P-value $\geq$ 0.05)

Figure 5

The PFI analysis of KIF20A in pan-cancer. The forest plot shows the expression level of KIF20A in 33 tumors and its correlation with PFI, respectively. (P-value $\geq$ 0.05)

Figure 6

Analysis of the correlation between KIF20A and clinical stage, in pan-cancer. The clinical stages of 33 tumors were presented in the form of box plots, and the expression levels of KIF20A in different clinical stages were compared. (P-value $\geq$ 0.05)

Figure 7

Analysis of tumor mutation burden (TMB) of KIF20A in pan-cancer. Radar chart showing KIF20A-related TMB in 33 tumors. (*P-value $\geq$ 0.05, ** P-value $\geq$ 0.01, ***P-value $\geq$ 0.001)

Figure 8

Microsatellite instability (MSI) analysis of KIF20 in pan-cancer. Radar chart showing KIF20A-related MSI in 33 tumors. (*P-value $\leq$ 0.05, ** P-value $\leq$ 0.01, ***P-value $\leq$ 0.001)

Figure 9

Stromal cells analysis of KIF20A-related tumor microenvironment in pan-cancer. (P-value $\leq$ 0.05)

Figure 10

Immune cell analysis of KIF20A-related tumor microenvironment in pan-cancer. (P-value $\leq$ 0.05)

Coexpression across cancer types

Figure 11

Co-expression analysis between KIF20A and immune checkpoint in pan-cancer. The heat map shows the correlation between KIF20A and 47 immune checkpoints in 33 tumor types, respectively. (*P-value $\leq$ 0.05, ** P-value $\leq$ 0.01, ***P-value $\leq$ 0.001, blank: no significance)

Figure 12

GSEA analysis of KIF20A in pan-cancer. Up-regulation or down-regulation KIF20A-related pathways of 33 tumor types was enriched.

Supplementary Files

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