A Pan-Cancer Analysis of the KIF Family Gene and their Association with Prognosis, Tumor Microenvironment, and Therapeutic Targets

Qitong Xu

The First Affiliated Hospital with Nanjing Medical University

Yiming Guo

Eye Hospital of Wenzhou Medical University

Feng Xu

The First Affiliated Hospital with Nanjing Medical University

Xu Zhang

The First Affiliated Hospital with Nanjing Medical University

Mengyuan Cai

The First Affiliated Hospital with Nanjing Medical University

Chuang Yang

The First Affiliated Hospital with Nanjing Medical University

Yuzhou Huang

The First Affiliated Hospital with Nanjing Medical University

Mian Zhang

First Affiliated Hospital of Soochow University

Jifu Wei

Jiangsu Cancer Hospital

Qiang Ding (✉ dingqiang@njmu.edu.cn)

The First Affiliated Hospital with Nanjing Medical University

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Abstract

Background: Recently, studies have shown that kinesins(KIF) play an important role in the occurrence and development of many tumors. However, there is no complete understanding of the role of KIF family in Pan cancer, and its role in the immunity and tumor microenvironment (TME) is unclear.

Methods: Based on TCGA database and integrated several R packages, we explored the relationship between the expression of KIF genes and patient survival, immune subtypes, TME, tumor stem cell correlation, and drug sensitivity in cancer.

Results: We use nine highly expressed KIF genes(KIF2C, KIF4A, KIF7, KIF11, KIF14, KIF18A, KIF18B, KIF20A, KIF20B) to represent whole KIF family. The change in KIF gene expression was significantly related to overall survival. The nine KIFs' high expression is accompanied by the up-regulation of C1 immune subtype, which is related to cell proliferation and interruption of immune process. Further, KIF gene expression showed significant correlation and cancer cell stemness characteristics. Top25 relevant KIF-drug pairs were displayed according to their P values. We further discussed KIF family influence in Mesothelioma(MESO) and Sarcoma(SARC). The CIBERSORT results manifested that increased level of infiltration of B cells naive, Mast cells resting and NK cells activated could be used as a protective factor to promote survival.

Conclusions: Our study supplemented a complete map of the effect of KIF family in Pan cancer. We suggested that KIF family may be a potential target for cancer therapy.

Introduction

In recent years, cancer has become the biggest problem perplexing human health, but there is still a lack of effective consensus treatment at the level of Pan cancer. The exploration of anti-tumor therapeutic targets is the basis for accurate and effective cancer treatment. The spindle has been verified as an effective therapeutic site in cancer chemotherapy^[1]. Some of well-known anti-proliferative agents, including paclitaxel and docetaxel, both of which target Microtubule (MT), are clinically successful anti-cancer agents for certain types of cancer^[2]. However, considering that these drugs have certain limitations, such as drug resistance and dose-dependent side effects^[3]. Therefore, it is necessary to block the formation of the spindle during cell division from other angles.

Kinesins(KIF), a superfamily with more than 650 members identified, exist in all eukaryotes and act as molecular motors that travel unidirectionally along microtubule tracks to fulfil their many roles in intracellular transport or cell division. The human genome contains about 45 different KIFs, all of which share a highly conserved motor domain that provides motor binding to microtubules^[6], and they can be grouped into 14 subfamilies based on their molecular structure. Functionally, they participates in the different stages of cell division and the transport of intracellular vesicles and organelles in eukaryotic cells^[7,8].

Recently, studies have shown that kinesins play an important role in the occurrence and development of tumors^[4]. For example, KIFC3/C1/1A/5A were found to mediate resistance of docetaxel in breast cancer cells^[9]. KIF20A was transcriptionally regulated by FOXM1 in ovarian cancer and the knockdown of KIF20A decreased the proliferation and invasion of ovarian cancer cells^[10]. The development of bioinformatics has enriched the means of screening and exploring KIF family in the process of tumor development, and KIFs have been researched in breast cancer^[11], renal clear cell carcinoma^[12], lung adenocarcinoma^[13], liver cancer^[14].

However, so far there is no report on systematic analysis of KIF members from the perspective of pan-cancer. Considering the important role of kinesins in tumorigenesis and development, it is very necessary to study the global effect of KIF members in tumors from a broader perspective. Therefore, we comprehensively analyzed the expression characteristics of all members of KIF family in various types of cancer by using the multiple database based on TCGA in this study. We identified KIF molecules that are of universal significance in various tumors and further analyzed their potential biological functions and common characteristics. In addition, we also evaluated their clinical value and their role in the process of immune infiltration from the perspective of both Pan cancer and single cancer.

Results

Expression of KIF members in pan-cancer

To explore the heterogeneity of the KIF members, we detected the expression level of KIF members in all 33 cancer types in TCGA pan-cancer data. Our results indicated that almost all KIF genes have certain degree of overexpression in cancers (Figure 1A). Further analysis showed that the expression of some KIF genes, such as KIF1A, KIF5A and KIF5C are significantly reduced in GBM and KICH, while these KIF members are highly expressed in other tumors (Figure 1B). Then we calculated the significance level of KIF members in different cancers in the tumor samples and adjacent normal tissues. The heat map shows that the overexpression of most KIF genes in each cancer is significant (Figure 1C). In addition, KIF2C and KIFC1 are the two genes with the most significant positive correlation (Correlation coefficient = 0.94, Fig. 1D); KIF3C and KIF12 are the two genes with the most significant negative correlation (Correlation coefficient = -0.11, Fig. 1D). This indicates that a majority of KIF genes may involved in complex co-expression associations in different types of cancer.

Prognostic value of KIF genes in pan-cancer

We summarized the KIF genes that play a significant role in the prognosis of different tumors (Figure 3A). Whether a member of the KIF genes is a risk factor or a protective factor varies depending on the type of cancer. In some tumors, the KIF genes involved are completely oncogenes, including LIHC, ACC and SARC. Quite the opposite, the KIF genes in some tumors completely play a protective role, such as STAD and THYM. Considering the large number of genes in the KIF family and their consistent expression and prognostic trends in a variety of cancers, we screened out nine highly expressed KIF genes that were

significantly overexpressed compared to the normal control group and affected several cancer types. We plan to use this group of molecules(KIF2C, KIF4A, KIF7, KIF11, KIF14, KIF18A, KIF18B, KIF20A, KIF20B) to represent KIF members to analyze their impact on pan-cancer(Figure 3B). Then we showed the effect of each KIF representative molecule's expression level on the prognosis of specific cancers (Figure 2). We further investigated the nine KIF genes' prognosis risk in pan-cancer by COX analysis (Figure 3C-Table 1). This further confirms their consistency in carcinogenicity.

The nine-KIF genes is associated with immune response and TME

Six different types of immune infiltration have been found in human tumors, corresponding to tumor promotion and inhibition. They are C1 (wound healing), C2 (INF-r dominant), C3 (inflammation), C4 (lymphopenia dominant), C5 (immunologically quiet), and C6 (TGFB β dominant)^[18]. We correlated the immune infiltration in TCGA pan-cancer data with the expression levels of nine KIF members and visualized it (Figure 4A).

Through ESTIMATE algorithm to calculate the stromal and immune scores in pan-cancer, we also realized that these nine molecules' expression are closely related to stromal cells and immune infiltration levels^[17] (Figure 4B, 4C). Specifically, the KIF genes has a significantly negative correlation with stroma and immune scores. Since the stromal and immune score can be used to evaluate tumor growth, disease development, and drug resistance, the low scores shown by this group of KIF genes means that the high expression of nine KIF genes can reduce the heterogeneity of the microenvironment and promote the purity of tumor cells, thereby reducing tumor malignancy, despite the fact that each gene different ratings. Nevertheless, this overall negative correlation is in contradiction with the effects of some KIF members as cancer-promoting genes to reduce survival rates. These contradictory results and the diversity of association between different KIF genes expression level and the Estimate scores of the different cancers in TCGA may be the result of the potential mechanisms related to different biological characteristics. And this positive effect of immune infiltration in the tumor microenvironment exerted by them can provide ideas for new treatment methods.

The nine-KIF genes is associated with tumor stem cells and chemosensitivity

In the process of cancer development, tumor cells gradually lose the characteristics of adult cells and gradually dedifferentiate into a state of primitive cells^[21]. This process can be evaluated by the stemness index, and the increase in stemness index will be accompanied by more active biological processes, such as high metabolism, high differentiation and high metastasis, which will increase risk of death. Stemness index includes RNA stemness score (RNAss) based on mRNA expression and DNA stemness score (DNAss) depending on the DNA methylation pattern, both of which are performed by Spearman correlation tests (Figure 5A, 5B). Then we detect the correlation between tumor stem cell characteristics and the nine KIF genes expression by these quantitative indicators. The result shows that KIF gene expression has a significantly positive correlation with RNAss and DNAss in pan-cancer, though the opposite trend is shown in Thymoma (THYM) and Kidney renal clear cell carcinoma(KIRC)-this may be

related to the heterogeneity of different tumors (Figure 5A, 5B). Considering that the expression of these nine genes is related to stemness, we further explored their relationship with drug resistance. Here, we sort the first 25 most relevant ones according to their P values (Figure 5C). It is found that they are significant relevance. Especially as the expression of KIF18B and KIF20B increases, drug sensitivity also increases significantly.

Role of the KIFs in MESO and SARC

Because most of the KIF genes involved in Mesothelioma(MESO) and Sarcoma(SARC) are risk factors which means poor survival, we further discussed their influence on the occurrence and development of these tumors by taking these nine KIF genes as representatives.

Figure 1 has shown that there is a significant difference in the expression of all KIF genes between MESO and SRAC tumors and adjacent normal cells. We further determined the correlation between the group of genes and various immune subtypes in the two kind of tumors' TME. The results showed that there were significant differences among different immune subtypes of the nine KIF genes (Figure 6A, 6B).

At the same time, we calculated other immune infiltration and stemness indicators in MESO and SARC, and evaluated the impact of these KIF molecules(Figure 6C, 6D). We also found that the KIF genes that are significantly differently expressed in SARC are all risk factors (Figure 1B, 6D). Especially the high expression of KIF18A and KIF20A significantly reduced survival time(Figure 2).

In addition, by using the CIBERSORT algorithm, we constructed 22 types of immune cell maps of 162 SARC samples (161 tumor samples/ 1 normal tissue sample) and 55 MESO samples and analyzed the correlation between immune cells(Figure 7).

Discussion

KIF carry out two major, non-mutually exclusive roles in eukaryotic cells: they are important at different stages of cell division and they are crucial for intracellular vesicle and organelle transport^[23,24]. To fulfil their many roles, kinesins move unidirectionally along micro-tubules and are driven by ATP hydrolysis. Previous research has shown that KIFs mainly act on the spindle during cell division, so it is widely used as the target of anti-tumor chemotherapy drugs^[25].

In this study, we explored the expression of the KIF gene in 33 different tumors as well as para-cancerous or normal tissues, using independent data sets from TCGA.

We have seen a trend of widespread over-expression of this gene family in pan-cancer, and most of the KIF genes in different cancers are highly significant compared with normal controls, though there was significant heterogeneity in KIF genes expression between different tumor types and within each tumor type(Figure 1).

Our current study also identified the relationship between KIF family gene expression level and pan-cancer prognosis in different tumors (Figure 2, 3). And the result shows that most of them have shown prognostic value in a variety of cancers, and most of the genes are oncogenes. For example, the expression of KIF1B and KIF13A are protective factors, while KIF2C and KIF20A will reduce the survival rate. For example, in KIRC, the expression of KIF1B and KIF13A are protective factors, while KIF2C and KIF20A will reduce the survival rate. The same KIF gene may play opposite roles in different tumors. For example, the increased expression of KIF20B in KIRP will reduce the survival rate, while in THYM, it will show the opposite trend. However, considering the large number of genes in this family and the consistent overall trend of the effects, we selected nine KIF genes based on their expression levels, the significance of their roles in different tumors, and their broader influence as cancer-promoting genes. These genes were used as representatives to evaluate the KIF members impact on tumors. And this group of genes is displayed by the forest map under cox analysis-showing typical and consistent characteristics.

As the environment where tumor cells survive, TME is a part of tumorigenesis and development and is deeply involved in the process^[26,27]. In detail, the microenvironment provides the material conditions needed for tumor survival, and tumor cells continue to influence or even transform the microenvironment during the growth process^[27]. And the indispensable accompanying biological process in tumorigenesis is also of great significance for the diagnosis, prognosis and even treatment of the disease^[28,29]. The ESTIMATE algorithm based on single sample Gene set Enrichment Analysis can quantify the effect of KIF genes on TME and immune infiltration^[17].

The outcomes of our transcriptome analysis on the pan-cancer data from the TCGA database show that the expression of nine KIF genes is negatively correlated with tumorigenesis (Figure 4). Noticeably, the ratio of stromal and immune components in TME in ACC is negatively correlated with the expression of related KIF genes. This may be contradictory to the fact that their high expression will reduce survival rate, but perhaps the complex mediation network of KIF and the heterogeneous properties of tumors explain this to some extent.

Besides, we also analyze the potential correlation between the nine KIF genes expression and immune subtype in pan-cancer (Figure 5). The results showed that all the highly expressed KIF genes were related to the up-regulation of C1. This not only corresponds to the molecular functions of the KIF family itself and the previous target of tumor-based chemotherapeutics to interfere with cell division^[4], but also suggests new treatment ideas from the perspective of immune cycle disruption—which can drive immune evasion^[18]. It can be noted that the features associated to the immunophenotypes of lower cytotoxicity are suited to be targeted by existing drugs. And the lower antitumor pressure exerted by these immunophenotypes also allows the growth of more tumor clones, resulting in more heterogeneous malignancies with greater metastatic potential^[30]. However, this idea still needs to be confirmed by further experiments.

The stemness of tumors means some of the characteristics of cancer cells: de-specificity and maintain high division, high metabolism, low intercellular adhesion and other active biological processes. The stemness index is related to tumor pathology, immune microenvironment content, intratumor heterogeneity and drug targets^[21]. By applying an innovative one-class logistic regression (OCLR) machine-learning algorithm, the characteristics of tumor stem cells can be measured via RNA stemness score (RNAss) and DNA stemness (DNAss)^[30]. Our results show that although the nine KIF molecules screened out show varying degrees in different tumors, the overall trend still shows a consistent negative correlation with RNAss and DNAss. This means that increased expression of KIF molecules can weaken the stemness characteristics of tumors. Then the further evaluation of the relationship between their expression and drug resistance, shows that they have a strong correlation.

It is worth noting that, in addition to the high expression of C1 and C2 subtypes in MESO and SARC as in pan-cancer, C4 and C6 subtypes are also generally increased (Figure 6). This can provide new means for the exploration of new therapeutic targets, including immune checkpoint modulators applied to cancer patients^[22].

The CIBERSORT results manifested that in the two types of immune cells with the strongest positive correlation were CD8 T cells and T cells follicular helper ($r=0.59$), and the two types of immune cells with the strongest negative correlation were Macrophages M1 and Macrophages M0 ($r=-0.44$). It is also worth noting that the level of infiltration of B cells naive, Mast cells resting and NK cells activated is significant to the survival level, and the high infiltration level can be used as a protective factor to promote survival (Figure 7).

Conclusion

Although we have described the role of KIF gene in tumors in terms of expression, prognosis, immunity, dryness and drug resistance, there are still the following shortcomings in this study. First of all, this study analyzes the KIF gene completely from the perspective of bioinformatics, and lacks the corresponding in vivo and in vitro experimental support. Therefore, in the future, follow-up molecular and cell experiments are needed to further verify the conclusions of the corresponding high-throughput data analysis. In addition, considering the possible problems when the TCGA database includes data-this is unavoidable in further analysis, such as the inclusion ratio of data of different races and the way of integrating clinical information difference for various tumors. The corresponding information bias needs to be improved by integrating more database data. Future prospective studies of KIF family genes expression and immune cell infiltration in various tumors may help to provide mechanistic insights with the topic.

Methods

Data sources

The gene expression RNAseq (HTSeq-FPKM), clinicopathological data, immune subtype, survival data, stemness score (RNA based), and (DNA methylation-based) of 33 cancers were downloaded from the online database UCSC Xena (<https://xena.ucsc.edu/>, originated from TCGA database)^[15].

Expression level, difference analysis, and correlation analysis of the MEIS family genes in pan-cancer

We visualized the expression of the KIFs in TCGA cancers using a boxplot graph. Next, based on log2 (fold change), we drew heatmaps of 18 tumor types with more than five adjacent normal samples to show the difference in KIF gene expression between primary tumors and adjacent normal tissues. Finally, we used Spearman's correlation test to calculate the gene expression correlation of KIF members in 33 cancer types. "Wil-cox.test" was applied to analyze the differential KIF family gene expression in different cancer types. "*", "**", "***", indicate P-value<0.05, <0.01, <0.001, respectively. A box plot and heatmap were further designed using the R-package "ggpubr" and "pheatmap" respectively. Correlation analysis among KIF family genes were performed by R-package "corrplot".

Selection of nine representative KIF genes

Because almost all KIF members are highly expressed in 33 cancers of TCGA, we first base on the KIF genes whose average expression value is greater than 1. Then select the KIF gene that is highly significant in the specific tumor compared to the normal control group. Take the intersection of the two KIF genes and cross them with the KIF genes that are widely involved in tumor prognosis (≥ 5), and finally get 9 KIF genes that are widely representative.

The relationship between the KIF members and survival rate of patients

Obtain each sample's survival data from the TCGA database and further analyze the relationship between expression of KIF genes and clinical outcome. Overall Survival (OS) was adequately evaluated. The survival analysis was assessed by the Kaplan-Meier method and the log-rank test ($P < 0.05$). The median expression level of KIF genes was selected as the cut-off value of the human cancer dichotomy so that each patient was divided into high-risk and low-risk groups. According to the high and low-risk value, a survival curve was delineated by the R-package "survminer" and "survival". Besides, we also conducted a COX analysis(Cox proportional hazards regression model) to identify the association between the nine KIF genes expression and prognosis of pan-cancer. Finally, the forest plot was drawn using the R-package "survival" and "forestplot".

Correlation analysis of immune infiltration and TME

The analysis of variance was used to test the correlation between the nine KIF genes expression and immune infiltrating subtypes in all cancer types to further understand the relationship between KIF members and immune components in tumors. We used the ESTIMATE algorithm to score the stroma and immunity of each sample. We then used the Spearman correlation test to analyze the infiltration level of immune and stromal cells in different tumors^[17].

Correlation analysis of tumor stemness and drug sensitivity analysis

To explore the characteristics of various tumor stem cells, we extracted the transcriptome and epigenetic methylation data of TCGA tumor samples. We then performed Spearman correlation tests to detect the correlation between tumor stem cell characteristics and MEIS expression. In addition, we downloaded the data of different cancer cell lines from the NCI-60 database (<https://discover.nci.nih.gov/cellminer/>) and used the Pearson correlation test to explore the relationship between the KIF genes expression and drug sensitivity. We included 263 drugs approved by the FDA or drugs in clinical trials for correlation analysis. Data processing and result visualization were performed using R package “impute”, “limma”, “ggplot2”.

Relationship between KIF members and Mesothelioma(MESO) and Sarcoma(SARC)

In order to explore the correlation between KIF genes' expression and a certain type of cancer that we are concerned about (MESO and SARC in this study), we analyzed and visualized the correlation between the representative nine KIF genes and immune subtypes, clinical characteristics, TME, and stem cells of a single tumor. In addition, to further explore the content of immune cells in a certain type of cancer, we used the CIBERSORT calculation method to analyze the proportion of tumor-infiltrating immune subsets. At the same time, quality filtering was performed, in SARC, 161 tumor samples and 1 normal tissue sample with $P < 0.05$ were analyzed in a mixed expression matrix.

Statistical analysis

Statistical analyses were performed using the R v.4.0.2 (<https://www.r-project.org/>). The linear mixed-effects model was used to analyze the differences in gene expression between tumor and normal tissues. Univariate and multivariate Cox regression analyses or the Log-rank test were used to investigate the relationship between gene expression and the patients' overall survival. The association between gene expression and the stemness, stromal, immune, and estimate scores, as well as drug sensitivity, was given via the calculation of Spearman's or Pearson's correlation coefficients. In addition, linear regression was used to investigate the relationship between gene expression and the patients' clinical characteristics, immune components, and MESO and SARC subtypes. Statistical significance is defined as $P < 0.05$.

Ethical statement

All procedures performed in this study were in accordance with the Declaration of Helsinki (as revised in 2013) and no ethical approval was required because the data we used were obtained from public databases. Because of the retrospective nature of the research, the requirement for informed consent was waived.

Abbreviations

Kinesin family(KIF); tumor microenvironment (TME); Mesothelioma(MESO); Sarcoma(SARC); The cancer genome atlas(TCGA); RNA stemness score (RNAss); DNA stemness score (DNAss); Thymoma(THYM); Kidney renal clear cell carcinoma(KIRC); Overall Survival (OS); Cox proportional hazards regression model (COX); One-class logistic regression (OCLR).

Declarations

Consent for publication

Written informed consent for publication was obtained from all participants.

Availability of data and materials

All the original data in the article are obtained from the public database. Statistical analyses were performed using the R v.4.0.2 (<https://www.r-project.org/>).

Competing interests

The authors declare that they have no conflict of interest.

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Not applicable.

Authors' contributions

Qitong Xu and Yiming Guo did the analysis and prepared figures 1-7 and table1; Qitong Xu,Yiming Guo and Feng Xu wrote the main manuscript text; Xu Zhang, Mengyuan Cai, Chuang Yang and Zhang Mian prepared data; Qiang ding and Jifu Wei provided guidance for the subject; All authors reviewed the manuscript.

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Tables

Table 1 The nine KIF genes' prognosis risk in pan-cancer by COX analysis

Gene	Cancer	HR	HR.95L	HR.95H	P-value
KIF2C	LGG	1.692	1.478	1.936	2.19E-14
	KIRC	2.142	1.756	2.613	5.74E-14
	KIRP	2.768	2.072	3.697	5.44E-12
	ACC	2.398	1.813	3.172	8.77E-10
	MESO	2.137	1.642	2.780	1.58E-08
	LIHC	1.586	1.346	1.869	3.77E-08
	KICH	2.708	1.707	4.298	2.34E-05
	PAAD	1.577	1.222	2.034	4.59E-04
	UCEC	1.497	1.177	1.903	9.94E-04
	LUAD	1.210	1.067	1.373	3.01E-03
KIF4A	LGG	1.788	1.549	2.064	2.04E-15
	KIRP	3.516	2.557	4.834	1.02E-14
	KIRC	2.208	1.786	2.728	2.30E-13
	MESO	2.378	1.767	3.200	1.09E-08
	ACC	3.329	2.147	5.162	7.66E-08
	LIHC	1.447	1.229	1.705	9.78E-06
	KICH	2.722	1.729	4.288	1.55E-05
	PAAD	1.831	1.342	2.498	1.34E-04
	LUAD	1.294	1.126	1.487	2.74E-04
	SARC	1.272	1.062	1.524	8.89E-03
KIF7	KIRC	2.198	1.595	3.028	1.47E-06
	COAD	2.442	1.560	3.822	9.41E-05
	MESO	1.879	1.361	2.595	1.29E-04
	KICH	6.929	2.462	19.497	2.45E-04
	THYM	0.193	0.066	0.559	2.43E-03
	UVM	0.250	0.101	0.623	2.91E-03
	ACC	1.629	1.143	2.323	6.98E-03
	KIRP	1.990	1.187	3.337	9.07E-03
	UCEC	1.433	1.076	1.909	1.39E-02
	HNSC	1.297	1.046	1.610	1.80E-02
KIF11	KIRP	3.123	2.303	4.237	2.43E-13
	ACC	3.558	2.380	5.320	6.21E-10
	KIRC	1.926	1.494	2.483	4.17E-07
	MESO	2.051	1.537	2.737	1.04E-06
	LGG	1.496	1.262	1.774	3.60E-06
	KICH	6.315	2.783	14.329	1.04E-05
	PAAD	2.209	1.534	3.179	2.01E-05
	LIHC	1.531	1.249	1.876	4.07E-05
	PCPG	5.292	2.311	12.119	8.10E-05
	LUAD	1.304	1.120	1.518	6.03E-04
KIF14	LGG	2.246	1.815	2.779	9.59E-14
	KIRP	5.526	3.484	8.764	3.73E-13
	KIRC	4.016	2.746	5.873	7.53E-13
	MESO	3.505	2.389	5.143	1.44E-10
	ACC	4.316	2.616	7.120	1.04E-08
	PAAD	3.402	1.948	5.942	1.68E-05
	KICH	10.896	3.519	33.733	3.44E-05
	UVM	59.983	6.601	545.080	2.77E-04
	LUAD	1.380	1.153	1.651	4.41E-04
	LIHC	1.661	1.248	2.212	5.10E-04
KIF18A	KIRP	14.221	7.455	27.129	7.89E-16
	LGG	2.323	1.867	2.891	4.07E-14
	KIRC	3.198	2.279	4.488	1.78E-11
	ACC	6.460	3.520	11.857	1.72E-09
	LIHC	2.148	1.620	2.848	1.09E-07
	KICH	11.368	4.150	31.139	2.27E-06
	PCPG	103.030	10.996	965.401	4.91E-05
	PAAD	2.441	1.582	3.767	5.55E-05
	LUAD	1.577	1.250	1.990	1.22E-04
	MESO	1.814	1.219	2.697	3.29E-03
KIF18B	KIRC	2.469	2.002	3.044	2.83E-17
	KIRP	4.075	2.827	5.873	4.96E-14
	ACC	5.296	3.126	8.972	5.71E-10
	MESO	2.102	1.608	2.748	5.50E-08
	LIHC	1.550	1.277	1.881	9.31E-06
	KICH	3.254	1.871	5.659	2.92E-05
	PAAD	1.768	1.271	2.460	7.17E-04
	LGG	1.303	1.103	1.540	1.85E-03
	UVM	4.506	1.527	13.294	6.39E-03
	PRAD	2.882	1.274	6.519	1.10E-02
KIF20A	KIRC	2.046	1.725	2.426	1.77E-16
	KIRP	3.681	2.684	5.048	6.14E-16
	LGG	1.774	1.525	2.063	1.13E-13
	LIHC	1.655	1.380	1.985	5.44E-08
	ACC	2.604	1.835	3.694	8.24E-08
	MESO	1.811	1.442	2.276	3.39E-07
	KICH	3.080	1.915	4.953	3.47E-06
	PAAD	2.164	1.547	3.028	6.58E-06
	LUAD	1.366	1.169	1.595	8.49E-05
	UVM	4.003	1.992	8.045	9.82E-05
KIF20B	ACC	5.510	2.981	10.184	5.19E-08
	BLCA	1.176	0.932	1.484	1.72E-01
	BRCA	1.038	0.808	1.334	7.72E-01
	CESC	1.220	0.824	1.807	3.21E-01
	CHOL	1.289	0.374	4.445	6.88E-01
	COAD	0.781	0.571	1.067	1.21E-01
	DLBC	1.076	0.433	2.674	8.75E-01
	ESCA	1.045	0.720	1.516	8.18E-01
	GBM	0.993	0.617	1.598	9.76E-01
	HNSC	0.994	0.798	1.237	9.55E-01

Figures

Figure 1

To explore the heterogeneity of the KIF members, we detected the expression level of KIF members in all 33 cancer types in TCGA pan-cancer data. Our results indicated that almost all KIF genes have certain degree of overexpression in cancers (Figure 1A). Further analysis showed that the expression of some KIF genes, such as KIF1A, KIF5A and KIF5C are significantly reduced in GBM and KICH, while these KIF members are highly expressed in other tumors (Figure 1B). Then we calculated the significance level of

KIF members in different cancers in the tumor samples and adjacent normal tissues. The heat map shows that the overexpression of most KIF genes in each cancer is significant (Figure 1C). In addition, KIF2C and KIFC1 are the two genes with the most significant positive correlation (Correlation coefficient = 0.94, Fig. 1D); KIF3C and KIF12 are the two genes with the most significant negative correlation (Correlation coefficient = -0.11, Fig. 1D). This indicates that a majority of KIF genes may be involved in complex co-expression associations in different types of cancer.

Figure 2

We plan to use this group of molecules(KIF2C, KIF4A, KIF7, KIF11, KIF14, KIF18A, KIF18B, KIF20A, KIF20B) to represent KIF members to analyze their impact on pan-cancer(Figure 3B). Then we showed the effect of each KIF representative molecule's expression level on the prognosis of specific cancers (Figure 2).

Figure 3

We summarized the KIF genes that play a significant role in the prognosis of different tumors(Figure 3A).whether a member of the KIF genes is a risk factor or a protective factor varies depending on the type of cancer. In some tumors, the KIF genes involved are completely oncogenes, including LIHC, ACC and SARC. Quite the opposite, the KIF genes in some tumors completely play a protective role, such as STAD and THYM. Considering the large number of genes in the KIF family and their consistent expression and prognostic trends in a variety of cancers, we screened out nine highly expressed KIF genes that were significantly overexpressed compared to the normal control group and affected several cancer types. We plan to use this group of molecules(KIF2C, KIF4A, KIF7, KIF11, KIF14, KIF18A, KIF18B, KIF20A, KIF20B) to represent KIF members to analyze their impact on pan-cancer(Figure 3B). Then we showed the effect of each KIF representative molecule's expression level on the prognosis of specific cancers (Figure 2). We further investigated the nine KIF genes' prognosis risk in pan-cancer by COX analysis (Figure 3CTable 1). This further confirms their consistency in carcinogenicity.

Figure 4

Six different types of immune infiltration have been found in human tumors, corresponding to tumor promotion and inhibition. They are C1 (wound healing), C2 (INF-r dominant), C3 (inflammation), C4 (lymphopenia dominant), C5 (immunologically quiet), and C6 (TGF β dominant)[18]. We correlated the immune infiltration in TCGA pan-cancer data with the expression levels of nine KIF members and visualized it (Figure 4A). Through ESTIMATE algorithm to calculate the stromal and immune scores in

pan-cancer, we also realized that these nine molecules' expression are closely related to stromal cells and immune infiltration levels[17] (Figure 4B, 4C). Specifically, the KIF genes has a significantly negative correlation with stroma and immune scores.

Figure 5

The result shows that KIF gene expression has a significantly positive correlation with RNAse and DNase activity in pan-cancer, though the opposite trend is shown in Thymoma (THYM) and Kidney renal clear cell

carcinoma(KIRC)-this may be related to the heterogeneity of different tumors (Figure 5A, 5B). Considering that the expression of these nine genes is related to stemness, we further explored their relationship with drug resistance. Here, we sort the first 25 most relevant ones according to their P values (Figure 5C). It is found that they are significant relevance. Especially as the expression of KIF18B and KIF20B increases, drug sensitivity also increases significantly.

Figure 6

The results showed that there were significant differences among different immune subtypes of the nine KIF genes (Figure 6A, 6B). At the same time, we calculated other immune infiltration and stemness indicators in MESO and SARC, and evaluated the impact of these KIF molecules (Figure 6C, 6D). We also found that the KIF genes that are significantly differently expressed in SARC are all risk factors (Figure 1B, 6D).

Figure 7

In addition, by using the CIBERSORT algorithm, we constructed 22 types of immune cell maps of 162 SARC samples (161 tumor samples/ 1 normal tissue sample) and 55 MESO samples and analyzed the correlation between immune cells(Figure 7).