ISSN 2706-6819 Vol.6, Issue 5: 48-54, DOI: 10.25236/IJFM.2024.060508

Comprehensive pan-cancer analysis identified GAB2 as a prognostic biomarker

Jin Chen[1], Pinzhi Dong[1], Yuan Ke[1], Langlang Zhang[1], Yuhan Yang[1], Yingnong Wu[1], Yudi Jin[1], Jihong Feng[2,*], Junmin Luo[1,*]

[1]Department of Immunology, Zunyi Medical University, Zunyi, China
[2]Department of Oncology, The Sixth Affiliated Hospital of Wenzhou Medical University, Lishui People's Hospital, Lishui, China
[*]Corresponding author

Abstract: *GAB2 is closely associated with the development of a variety of tumors. However, the detailed function and role of GAB2 in pan-cancer are largely unknown and require further in-depth investigation. Consequently, this study aims to investigate the biological functions of GAB2, and its potential to predict prognosis in pan-cancer. We applied multiple public databases such as TCGA, TIMER, GTEx, and CCLE to explore GAB2 expression in tumors. Univariate Cox regression and Kaplan-Meier survival analysis were used to detect the effects of GAB2 on OS, DSS, DFI, and PFI in these patients. It turns out that GAB2 expression was elevated in most tumor tissues compared to normal tissues, and was positively or negatively correlated with the prognosis of different tumors. Generally, comprehensive pan-cancer analysis identified GAB2 as a prognostic biomarker.*

Keywords: *GAB2, prognosis, pan-cancer, the Cancer Genome Atlas*

1. Introduction

Cancer development is a complex process involving numerous signaling networks and genes[1-2]. The pan-cancer analysis is the cross-sectional comparison of certain properties across many tumor types using bioinformatics analytic techniques, to apply diagnosis and treatment to a broader variety of tumors due to cross-tumor similarity[3]. With the rapid development of sequencing technology and the construction of online databases in recent years, a significant influx of data has provided the foundation for comprehensive pan-cancer analysis to guide tumor diagnosis and treatment. As a result, identifying important genes that differ between cancer types can aid in cancer diagnosis and treatment.

GAB family proteins are a group of highly conserved scaffold proteins, a class of substrate molecules that can bind to tyrosine kinases, and participate in the activation and conduction of multiple signaling pathways by recruiting some signal molecules rich in the phosphotyrosine domain[4-6]. The GAB family consists of five main members: GAB1, GAB2, and GAB3 of mammalian origin, as well as Dos and Soc1 proteins of Drosophila and Caenorhabditis elegans origin[7-9]. The Grb associated-binding protein (GAB2) is a crucial member of the GAB family that controls numerous signaling pathways to play a role in cell migration, adhesion, adhesion molecule production, and cytoskeleton creation (e.g. Ras/ERK pathway, PI3K/Akt/mTOR, etc.)[10].

As a scaffolding protein that binds to a variety of receptors and participates in multiple signaling pathways, including PI3K/AKT, SHP2/ERK, and JAK/STAT, it has recently been discovered to be highly expressed in human malignancies, including leukemia, breast, ovarian, liver, colorectal, and melanoma. This has an impact on the biological behavior of tumors[10-14]. Additionally, GAB2 plays a wide variety of regulatory roles in cancer and is intimately linked to molecules or pathways that control the disease and are crucial for the treatment of cancer. Therefore, through a thorough pan-cancer investigation, we hope to clarify the function of GAB2.

2. Manuscript Preparation

2.1. GAB2 Expression Pattern in Human Pan-Cancer

Concerning 33 different forms of cancer, the TCGA, a cornerstone of the cancer genomics

ISSN 2706-6819 Vol.6, Issue 5: 48-54, DOI: 10.25236/IJFM.2024.060508

initiatives, had characterized more than 20,000 original cancer samples and comparable non-carcinoma samples. The University of California Santa Cruz (UCSC) cancer genome browser was used in the current work to get the TCGA-processed level 3 RNA-sequencing data sets and the related clinical annotations (https:// tcga.xenahubs.net, accessed April 2020). The enormous variety of human cancer models has been thoroughly genetically and pharmacologically defined by the CCLE public initiative (https://portals.broadinstitute.org/ccle). The CCLE database, which has RNA-sequencing data sets for more than 1,000 cell lines, was used to conduct a more extensive analysis of differential gene expression in malignancies. For patients with 33 different cancer types, RNA sequencing data and clinical follow-up information were collected.

2.2. Pathological staging analysis

The GAB2 gene expression data in each sample were collected from the TCGA database and the samples from Solid Tissue. Normal blood, cancer-peripheral blood, and primary tumor were all screened further. After performing a log2 (x+0. 001) transformation on each expression value, cancer species with fewer than three samples in a single cancer species were excluded, and the expression data of 26 cancer species were obtained. R software (version 3.6.4) was used to calculate the expression difference between normal and tumor samples in each tumor, and the significance of the difference was determined using unpaired Wilcoxon rank sum and signed rank tests.

2.3. Prognostic Analysis

The relationship between GAB2 expression and patient prognosis, including overall survival (OS), disease-specific survival (DSS), disease-free interval (DFI), and progression-free interval (PFI), was investigated using forest plots and Kaplan-Meier curves in 33 kinds of cancer. Univariate survival analysis was used to compute the hazard ratios (HRs) and 95% confidence intervals.

3. Results

3.1. GAB2 Expression Analysis in Pan-Cancer

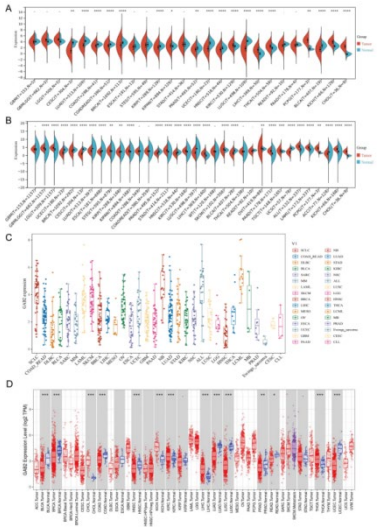

*Figure 1: Pan-cancer GAB2 expression. (A) GAB2 expression in tumor tissues from TCGA database. (B) Pan-cancer expression of GAB2 between tumor tissues from TCGA database and normal tissues from TCGA and GTEx database. (C) mRNA expression levels of GAB2 in various tumor cell lines from the CCLE database. (D) GAB2 expression in tumor tissues from TIMER database. The red and blue boxes represent tumor tissues and normal tissues, respectively. *p < 0.05; **p < 0.01; ***p < 0.001 and ****p < 0.0001; ns, not significant.*

First, we investigated the GAB2 expression in TCGA. GAB2 expression was found to be high in KIPAN, KIRC, LIHC, THCA, PCPG, KICH, and CHOL, but low in CESC, LUAD, COAD, COADREAD, BRCA, KIRP, PRAD, UCEC, HNSC, LUSC, and BLCA (Figure 1A). GAB2 was shown to be strongly expressed in GBMLGG, LGG, STES, KIPAN, STAD, KIRC, LIHC, SKCM, OV,

ISSN 2706-6819 Vol.6, Issue 5: 48-54, DOI: 10.25236/IJFM.2024.060508

PAAD, TGCT, ALL, LAML, PCPG, KICH, and CHOL 16 cancers when the TCGA and GTEx databases were combined. UCEC, BRCA, CESC, LUAD, ESCA, KIRP, PRAD, HNSC, LUSC, BLCA, UCS, and ACC are all downregulated (Figure 1B). CCLE research revealed that GAB2 had variable gene expression levels in various cancer cell lines, with SCLC, NB, ALL, and LCML showing comparatively high gene expression (Figure 1C). Finally, the TIMER database was used to assess GAB2 expression in pan-cancer. GAB2 expression was shown to be considerably higher in CHOL, KICH, KIRC, LIHC, and THCA tissues than in normal tissues (Figure 1D).

We evaluated GAB2 expression in patients with stage I, II, III, or IV cancers to measure gene expression levels throughout all tumor stages. Significantly different in tumors with ESCA, STES, KIPAN, KIRC, THYM, OV, TGCT, and SKCM (Figure 2 A-I).

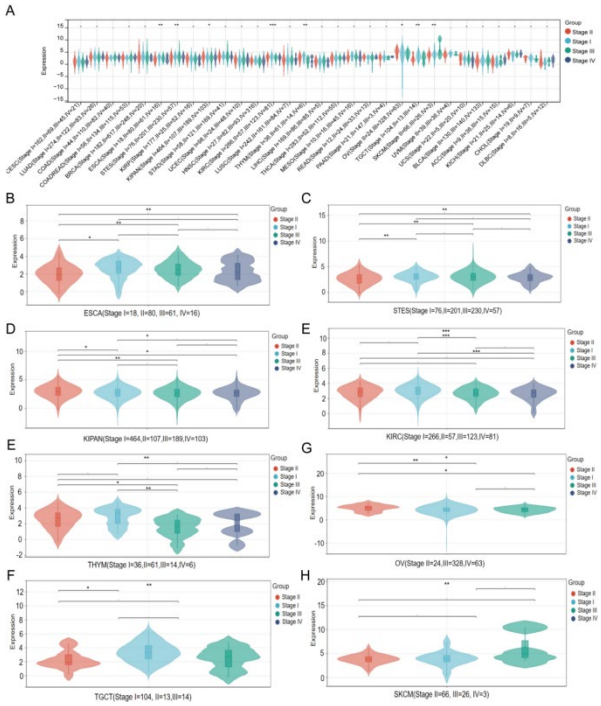

*Figure 2: Pan-cancer GAB2 expression in different WHO stages. (A-I) Pan-cancer differential expression of GAB2 in WHO stages in indicated tumor types from TCGA database. *p < 0.05; **p < 0.01; ***p < 0.001, and ****p < 0.0001; ns, not significant.*

3.2. Analysis of the relationship between GAB2 expression and prognosis

Using data from the TCGA database, we used single-variate Cox regression analysis to examine the relationship between GAB2 expression levels and OS in various cancer types. High GAB2 expression was found to be a risk factor for LUSC, SKCM-M, SKCM, and ACC using Cox regression. However, in GBMLGG, KIPAN, and KIRC, it proved to be a protective factor. The following survival studies, which used patient data dichotomized for the median expression value in each cancer type, demonstrate that survival differences in OS-related cancer types were all significant, indicating that patients with high GAB2 expression had poorer outcomes (Figure 3A-H).

ISSN 2706-6819 Vol.6, Issue 5: 48-54, DOI: 10.25236/IJFM.2024.060508

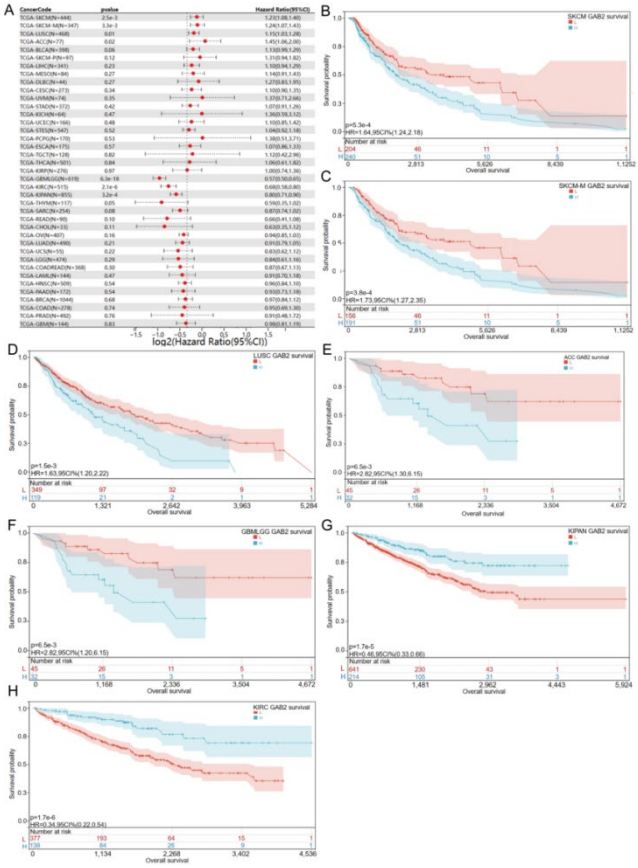

Figure 3: Association of GAB2 expression with patient overall survival (OS). (A) The forest plot shows the relationship of GAB2 expression with patient OS. (B-H) Kaplan-Meier analyses show the association between GAB2 expression and OS.

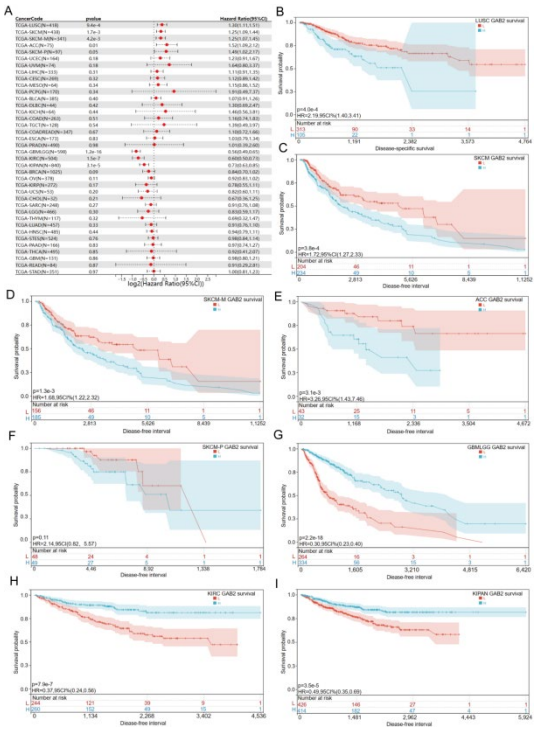

Figure 4: Association of GAB2 expression with patient disease-specific survival (DSS). (A) The forest plot shows the relationship of GAB2 expression with DSS. (B-H) Kaplan-Meier analyses show the association between GAB2 expression and DSS.

ISSN 2706-6819 Vol.6, Issue 5: 48-54, DOI: 10.25236/IJFM.2024.060508

High GAB2 expression was revealed as a risk factor in LUSC, SKCM-M, SKCM, and ACC by Cox regression analysis of DSS. It was, however, a protective factor in GBMLGG, KIPAN, and KIRC. The following survival studies, which used patient data dichotomized for the median expression value in each cancer type, demonstrate that survival differences in DSS-related cancer types were all significant and that patients with high GAB2 expression had poorer results (Figure 4A-I).

High GAB2 expression was discovered as a risk factor in ACC, LUSC, and CESC by Cox regression analysis, while it was a protective factor in GBMLGG, KIPAN, KIRC, and BRCA. The following survival analyses, which used patient data dichotomized for the median expression value in each cancer type, demonstrate that survival differences in PFI-related cancer types were all significant, indicating that patients with high GAB2 expression had poorer results (Figure 5A-H).

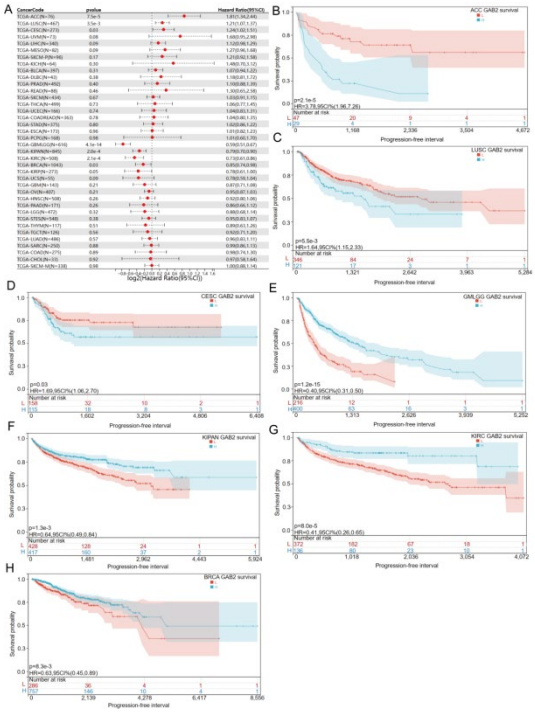

Figure 5: Association of GAB2 expression with patient progression-free interval (PFI). (A) The forest plot shows the relationship of GAB2 expression with PFI. (B-H) Kaplan-Meier analyses show the association between GAB2 expression and PFI.

Higher GAB2 expression was found to be a risk factor for ACC and LUSC in a Cox regression study of DFI (Figure 6A-C).

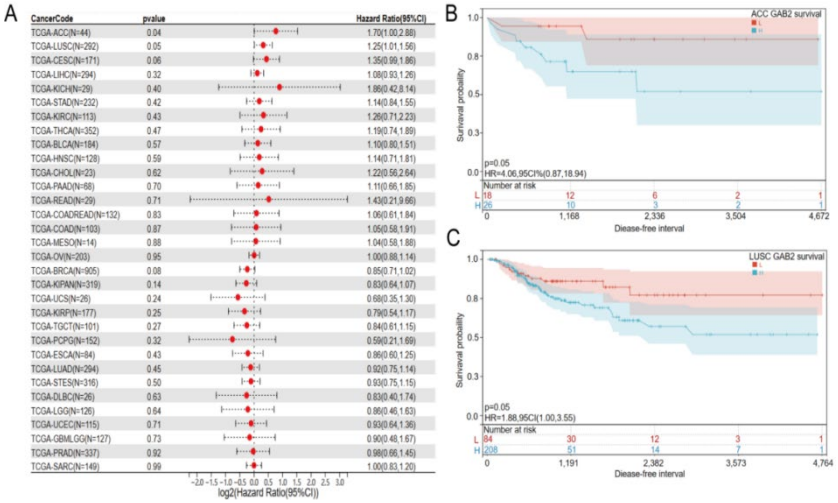

Figure 6: Association of GAB2 expression with patient disease-free interval (DFI). (A) The forest plot shows the relationship of GAB2 expression with DFI. (B) Kaplan-Meier analyses show the association between GAB2 expression and DFI.

ISSN 2706-6819 Vol.6, Issue 5: 48-54, DOI: 10.25236/IJFM.2024.060508

4. Discussions

GAB2 protein expression is aberrant in a variety of malignant tumors, including breast cancer, leukemia, melanoma, and ovarian cancer, according to existing research. Despite a wealth of experimental data on GAB2 and its signaling pathways, there are several complex regulatory mechanisms at work, and many questions remain unanswered[15]. As a result, we conducted a comprehensive pan-cancer analysis of GAB2 using multiple public databases, focusing on gene expression, mutation, and functional mechanisms, and our research contributes to a better understanding of GAB2's molecular mechanism to find new and more effective drug targets for clinical treatment of various tumors.

We discovered that the expression level of GAB2 changes in different malignancies and is closely associated with the prognosis of tumor patients in this study. GAB2 overexpression is a risk factor for SKCM, SKCM-M, LUSC, and ACC, as well as a protective factor for GBMLGG, KIRC, KIPAN, and BRCA. As a result, the expression effect of different tumor genes varies, necessitating additional molecular biology research.

We are committed to the GAB2 pan-cancer study in the hope of discovering common diagnostic and prognostic markers among malignancies, which will aid in tumor screening, diagnosis, tumor recurrence and metastasis monitoring, and tumor prognosis and efficacy assessment. The findings of this work give a preliminary foundation for understanding the GAB2 function, however, it has several limitations. More experimental data are needed to validate these findings and explain the distinct biological mechanism of GAB2 in various cancers using bioinformatics analysis.

5. Conclusions

Our research shows that GAB2 has value in the diagnosis and prognosis of a wide range of cancers and regulates cancer through a variety of mechanisms, which may contribute to understanding the role of GAB2.

Acknowledgments

This work was supported by the Program of Natural Science Foundation of Zhejiang Province (LY20H160017), Chinese Medicine Study Foundation of Zhejiang Province (2020ZB292) and PhD research startup foundation of Lishui People's Hospital (2020bs01).

References

[1] E Dolgin. Cancer's new normal[J]. Nat Cancer, 2021, 2(12): 1248-1250.
[2] A Mullard. Addressing cancer's grand challenges[J]. Nat Rev Drug Discov, 2020, 19(12): 825-826.
[3] N Wang, Zhu L, Wang L, et al. Identification of SHCBP1 as a potential biomarker involving diagnosis, prognosis, and tumor immune microenvironment across multiple cancers[J]. Comput Struct Biotechnol J, 2022, 203106-3119.
[4] S-J Adams, Aydin I-T, Celebi J-T. GAB2--a scaffolding protein in cancer[J]. Mol Cancer Res, 2012, 10(10): 1265-1270.
[5] R Gong, Li H, Liu Y, et al. Gab2 promotes acute myeloid leukemia growth and migration through the SHP2-Erk-CREB signaling pathway[J]. J Leukoc Biol, 2022, 112(4): 669-677.
[6] V Kondreddy, Magisetty J, Keshava S, et al. Gab2 (Grb2-Associated Binder2) Plays a Crucial Role in Inflammatory Signaling and Endothelial Dysfunction[J]. Arterioscler Thromb Vasc Biol, 2021, 41(6): 1987-2005.
[7] W Shioyama, Nakaoka Y, Higuchi K, et al. Docking protein Gab1 is an essential component of postnatal angiogenesis after ischemia via HGF/c-met signaling[J]. Circ Res, 2011, 108(6): 664-675.
[8] I Wolf, Jenkins B-J, Liu Y, et al. Gab3, a new DOS/Gab family member, facilitates macrophage differentiation [J]. Mol Cell Biol, 2002, 22(1): 231-244.
[9] G Sarmay, Angyal A, Kertesz A, et al. The multiple function of Grb2 associated binder (Gab) adaptor/scaffolding protein in immune cell signaling[J]. Immunol Lett, 2006, 104(1-2): 76-82.
[10] C Niu, Li M, Chen Y, et al. LncRNA NCAL1 potentiates natural killer cell cytotoxicity through the Gab2-PI3K-AKT pathway[J]. Front Immunol, 2022, 13970195.
[11] C Spohr, Poggio T, Andrieux G, et al. Gab2 deficiency prevents Flt3-ITD driven acute myeloid

ISSN 2706-6819 Vol.6, Issue 5: 48-54, DOI: 10.25236/IJFM.2024.060508

leukemia in vivo[J]. Leukemia, 2022, 36(4): 970-982.
[12] C Ding, Luo J, Li L, et al. Gab2 facilitates epithelial-to-mesenchymal transition via the MEK/ERK/MMP signaling in colorectal cancer[J]. J Exp Clin Cancer Res, 2016, 355.
[13] Y Yang, Wu J, Demir A, et al. GAB2 induces tumor angiogenesis in NRAS-driven melanoma[J]. Oncogene, 2013, 32(31): 3627-3637.
[14] J Cheng, Zhong Y, Chen S, et al. Gab2 mediates hepatocellular carcinogenesis by integrating multiple signaling pathways [J]. FASEB J, 2017, 31(12): 5530-5542.
[15] Gao X, Long R, Feng J., et al. Gab2 promotes the growth of colorectal cancer by regulating the M2 polarization of tumor-associated macrophages [J]. Int J Mol Med. 2024 Jan;53(1):3.