Prognostic Value and Immune Characteristics of RUNX Family in Human Cancers: A Pan-cancer Analysis

Han Zhao

Department of Ophthalmology, Eye, Ear, Nose, and Throat Hospital of Fudan University

Yun Chen

Department of Stomatology, the second Xiangya Hospital of Central South University

Peijun Shen

Department of Gastroenterology, The Third Xiangya Hospital of Central South University

Lan Gong (✉ 13501798683@139.com)

Department of Ophthalmology, Eye, Ear, Nose, and Throat Hospital of Fudan University

Research Article

Keywords: RUNX, pan-cancer, immune subtype, tumor microenvironment, prognoses, drug responses

Posted Date: August 12th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-659794/v1>

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Abstract

Background: Runt-related transcription factors (RUNX) are involved in numerous fundamental biological processes and play crucial parts in tumorigenesis and metastasis both directly and indirectly. However, the pan-cancer evidence of *RUNX* gene family is no available.

Methods: In this study, we analyzed the potential association between *RUNX* gene family expression and patient's prognosis, immune cell infiltration, drug response, and genetic mutation data across different types of tumors using based on The Cancer Genome Atlas, Gene Expression Omnibus, and Oncomine database.

Results: The results showed that the expression of the RUNX family varied among different cancer types, revealing its heterogeneity in cancers, and that expression of RUNX2 was lower than that of RUNX1 and RUNX3 across all cancer types. RUNX family gene expression was related to prognosis in several cancers. Furthermore, our study revealed a clear association between RUNX family expression and ESTIMATE score, RNA stemness, and DNA stemness scores. Compared with RUNX1 and RUNX2, RUNX3 showed relatively low levels of genetic alterations. RUNX family genes had clear associations with immune infiltrate subtypes, and their expression was positively related to immune checkpoint genes and drug sensitivity in most cases.

Conclusions: These findings will help to elucidate the potential oncogenic roles of RUNX family genes in different types of cancer and it can function as a prognostic marker in various malignant tumors.

1 Introduction

Runt-related transcription factors (RUNX) regulate many fundamental biological processes including proliferation, differentiation, apoptosis, and angiogenesis. According to structural analyses, RUNX family proteins have a highly conserved DNA-binding domain, called the Runt domain, and dimerize with a common non-DNA-binding partner known as core-binding factor subunit beta. There are three *RUNX* genes in the human genome, *RUNX1*, *RUNX2*, and *RUNX3*, which show distinct expression patterns across human tissues. RUNX1 is essential for hematopoiesis and is involved in the development of human leukemia. In addition to its role in leukemogenesis[1], RUNX1 is involved in sensory neuron diversification[2]. RUNX2 is involved in skeletal mineralization and frequently stimulates osteoblast differentiation of mesenchymal stem cells, promotes chondrocyte hypertrophy, and contributes to endothelial cell migration and vascular invasion of developing bones[3]. RUNX3 plays a part in controlling the growth and differentiation of gastric epithelial cells[4] and is expressed in cells of hematopoietic origin, including myeloid and B-cell lines and spleen cells[5].

In recent years, accumulating evidence has demonstrated that the *RUNX* gene family has crucial roles in tumor immunosuppression, determination of biological phenotypes, tumorigenesis, progression, metastasis, therapeutic effect, and patient prognosis, via both direct and indirect effects[6–9]. The *RUNX* gene family is intimately involved in carcinogenesis: the *RUNX1* gene was found to be mutated in human

leukemia[10]; and RUNX2 is overexpressed in osteosarcoma and regulates bone remodeling and osteoclast differentiation[11]. Importantly, RUNX2 is closely associated with drug resistance of various malignant cancers[12]. The *RUNX3* gene is located on chromosome 1p36, which is a hotspot depleted in various cancer types[13]. RUNX3 is expressed on various solid tumors and may contribute to tumor immunosuppression[14]. However, there is no human pan-cancer evidence of a potential role for the *RUNX* gene family in various tumor types.

With the rapid development of public databases, pan-cancer analysis can be used to profile any gene of interest and its associated clinical prognosis, as well as its potential molecular mechanisms in tumor and normal tissues. In this study, we conducted a pan-cancer analysis of *RUNX* gene family expression and patient prognosis across various types of cancer via public databases including the Cancer Genome Atlas (TCGA) and Oncomine. Furthermore, we provide RUNX family profiles with respect to immune cell infiltration, drug resistance, and genetic mutations, to assist clinicians to select appropriate therapeutic drugs and improve the prognosis of cancer patients.

2 Materials And Methods

2.1 TCGA data and processing

The publicly available TCGA database (<http://cancergenome.nih.gov>) contains the results of a landmark cancer genomics project, which has molecularly characterized over 20,000 primary cancer and normal samples spanning 33 cancer types up to 2021. The TCGA data included 33 different tumor types: adrenocortical carcinoma (ACC); bladder urothelial carcinoma (BLCA); breast cancer (BRCA); cervical squamous cell carcinoma and endocervical adenocarcinoma; cholangiocarcinoma (CHOL); colon adenocarcinoma (COAD); lymphoid neoplasm diffuse large B-cell lymphoma; esophageal carcinoma (ESCA); glioblastoma multiforme (GBM); head and neck squamous carcinoma (HNSC); kidney chromophobe (KICH); kidney renal clear cell carcinoma (KIRC); kidney renal papillary cell carcinoma (KIRP); acute myeloid leukemia (LAML); brain lower grade glioma (LGG); liver hepatocellular carcinoma (LIHC); lung adenocarcinoma (LUAD); lung squamous cell carcinoma (LUSC); mesothelioma (MESO); ovarian serous cystadenocarcinoma (OV); pancreatic adenocarcinoma (PAAD); pheochromocytoma and paraganglioma (PCPG); prostate adenocarcinoma; rectum adenocarcinoma (READ); sarcoma (SARC); skin cutaneous melanoma (SKCM); stomach adenocarcinoma (STAD); testicular germ cell tumors; thyroid carcinoma (THCA); thymoma (THYM); uterine corpus endometrial carcinoma (UCEC); uterine carcinosarcoma; and uveal melanoma (UVM). The UCSC Xena (<https://xenabrowser.net/>) website was used to collect RUNX family data from TCGA, including RNA sequencing results, clinical data, stemness scores, DNA methylation, and immune subtype data.

2.2 RUNX family expression analysis

The Oncomine database (www.oncomine.org) is a publicly accessible website server for genome-wide expression analysis, containing 715 datasets and 86,733 samples[15]. Here, we used Oncomine to investigate the expression levels of RUNX family members between various cancer tissues and adjacent normal tissues. In our experiments, student's t -test was used to analyze the differences in expression of RUNX family members in various types of cancer; a p -value of 0.05, a fold change of 2, and a gene rank in the top 10% were set as the significance thresholds.

We used the “ggpubr” R package to analyze the differential expression of RUNX family members between tumors and matched normal tissues in TCGA. In the pan-tumor analysis, gene expression was standardized. Fragments per kilobase million values were transformed into transcripts per kilobase million values. The results were visualized as heatmaps using the “pheatmap” R package.

2.3 Survival prognosis analysis

The Kaplan–Meier curves were used to analyze the correlation of the RUNX gene family and overall survival (OS), disease-specific survival (DSS), progression-free interval (PFI), and disease-free interval (DFI) across all TCGA tumors. We computed log-rank p -values and hazard ratios (HR) with 95% confidence intervals (95% CI). Data were visualized as forest plots (using the “forestplot” R package) and survival curves.

2.4 Mutation profiles

cBioPortal (www.cbioportal.org) is an interactive website that can be used to explore, visualize, and analyze multidimensional cancer genomics data[16]. Using the “Cancer Types Summary” module, we queried the copy number alterations and genetic alteration characteristics of the RUNX family on a pan-cancer basis. We obtained the alteration frequency, mutation type, and copy number alteration of the *RUNX* gene family across all tumors in TCGA via the “Cancer Types Summary” module of cBioPortal. We set “TCGA Pan Cancer Atlas Studies” in the “Quick select” section to query the genetic alteration characteristics of the *RUNX* gene family.

2.5 Tumor microenvironment and tumor stemness analysis

Tumor purity was assessed in 33 human cancers in TCGA using the “estimate” R package. Specifically, the ESTIMATE score is the sum of the immune and stromal scores, which represent the abundance of immune and stromal components, respectively. Higher ESTIMATE scores correspond to lower tumor purity. Six immune subtypes are used to measure immune infiltration in the tumor environment, as follows: C1 (wound healing), C2 [interferon (IFN)- γ dominant], C3 (inflammatory), C4 (lymphocyte depleted), C5 (immunologically quiet), and C6 [tumor growth factor β (TGF β) dominant]. Spearman's correlation analysis was used to reveal the relationships between the expression of RUNX family

members and the ESTIMATE immune and stromal scores. In addition, we measured tumor RNA stemness scores (RNAss) and DNA stemness scores (DNAss) from epigenetic and transcriptome data from TCGA. Specifically, RNAss is based on RNA sequencing data, and DNAss is calculated based on DNA methylation data. Spearman's correlation analysis was employed to investigate the correlations between the RUNX family and tumor stemness data. Pearson's correlation analysis was performed to analyze the correlations between TGFBI expression and immunoinhibitory and immunostimulatory gene subsets, tumor mutation burden (TMB), and microsatellite instability (MSI). The results were displayed as heatmaps using the "pheatmap" package in R.

2.6 Drug responses

The drug response data for the RUNX family were obtained from the National Cancer Institute (NCI)-60 database via the CellMiner database (<https://discover.nci.nih.gov/cellminer/home.do>). The NCI-60 database contains molecular and pharmacological data for a panel of 60 diverse human cancer cell lines. Pearson's correlation analysis was used to evaluate the association of RUNX family expression (based on transcript levels) with drug response (GI50). The drugs involved in the correlation analysis had all been identified by the Food and Drug Administration or drug clinical trials.

2.7 Protein–protein interactions

GeneMANIA (<http://www.genemania.org>) is an online resource that can be used to find genes that are related to a set of input genes, using a very large set of functional association data[17]. In this study, we input *RUNX1*, *RUNX2*, and *RUNX3* in the search module to evaluate the genes are functionally related to the RUNX gene family. These include protein-protein, protein-DNA and genetic interactions, pathways, reactions, gene and protein expression data, protein domains and phenotypic screening profiles.

2.8 Immunohistochemical analysis of TGFBI

The human protein atlas (HPA) cohort (<https://www.proteinatlas.org>) is a database that aims to map all human proteins in cells, tissues and organs level by integrating various omics technologies. In our study, HPA was used to illustrate RUNX family protein expression data from metastatic melanoma tissues and matched normal tissues.

2.9 Statistical analyses

Correlation analyses for the expression of RUNX family members between cancer and adjacent tissues were performed in Oncomine, with *p*-values, fold changes, and gene ranks. All analyses used R version 4.0.4, 64-bit (<https://www.r-project.org/>) and its appropriate packages. The survival results are displayed

with HR, 95% CI, and log-rank p -values. For all statistical analyses, $p < 0.05$ was considered statistically significant.

3 Results

3.1 Gene expression analysis of RUNX

To compare expression levels of RUNX family members between tumor and normal tissues, the mRNA levels of RUNX family members in tumors and matched normal tissues were analyzed via the Oncomine database. Our results showed relatively high expression of RUNX1 and RUNX2 in breast cancer, head and neck cancer, kidney cancer, leukemia, and pancreatic cancer. In addition, RUNX1 was also relatively higher in brain and central nervous system cancers, colorectal cancer, and sarcoma. The expression of RUNX3 was relatively higher in esophageal cancer, head and neck cancers, kidney cancer, lymphoma, and sarcoma (Figure 1A).

To further evaluate the differential expression of RUNX family members, we profiled and compared their expression across all TCGA tumors using the R software. Specifically, our results showed that RUNX1 expression was significantly elevated in BLCA, CHOL, COAD, ESCA, GBM, HNSC, KIRC, KIRP, LIHC, LUAD, READ, STAD, THCA, and UCEC. By contrast, lower RUNX1 expression was found in PARD (Figure 1B). RUNX2 showed higher expression in BLCA, BRCA, CHOL, ESCA, GBM, HNSC, KIRC, KIRP, LUAD, LUSC, STAD, and THCA but decreased expression in PARD (Figure 1C). RUNX3 expression was significantly elevated in ESCA, GBM, HNSC, KIRC, KIRP, LUAD, LUSC, STAD, and UCEC, but lower RUNX3 expression was found in BRCA, COAD, LIHC, LUAD, and THCA (Figure 1D).

We also analyzed the pan-cancer and inter-tumor heterogeneity of RUNX family expression; the results showed that RUNX1 and RUNX3 were highly expressed whereas RUNX2 was moderately expressed at the pan-cancer level (Figure 2A). As shown in Figure 2B, we observed significant heterogeneity in gene expression of *RUNX* gene family members across different tumor types in TCGA. Then, we analyzed the correlations among RUNX family members; RUNX1 and RUNX2 were the two genes with the most significant positive correlation (correlation coefficient = 0.66, Figure 2C).

3.2 Prognostic value of RUNX

In order to investigate the correlation of RUNX family expression with prognosis of patients across different tumor types, we performed Cox analysis. According to our results, all RUNX family members showed different expression associated with prognosis of patients. Specifically, RUNX1 had a detrimental role in UVM, LGG, MESO, KIRC, PAAD, GBM, KIRP, and OV (HR>1, $p < 0.05$); however, it had a protective role in SKCM, LUAD, BRCA, ESCA, and THYM (HR<1, $p < 0.05$). RUNX2 was detrimental in UVM, KICH, ACC, LGG, KIRC, BLCA, PAAD, MESO, GBM, and SARC (HR>1, $p < 0.05$) but protective in SKCM (HR<1, $p < 0.05$). In addition, higher expression of RUNX3 was associated with poor survival outcomes in LGG and COAD

(HR>1, $p<0.05$, Figure 3). Detailed results of the Cox analysis of the RUNX family across the TCGA database are summarized in Supplementary Table S1.

In order to understand the prognostic value of the *RUNX* gene family, we used Kaplan–Meier survival curves to determine patient OS based on the clinical information downloaded from TCGA. Of the three family members, RUNX1 predicted the best prognosis in patients with BRCA, ESCA, and SKCM (all $p<0.05$, Figure 4A-C). By contrast, RUNX1 predicted poor prognosis in patients with KIRC, KIRP, LGG, MESO, OV, and UVM (all $p<0.05$, Figure 4D-I). RUNX2 had a protective role in PCPG and SKCM (all $p<0.05$, Figure 4J-K). On the other hand, RUNX2 had a detrimental role in seven cancer types: BLCA, KIRC, KICH, LGG, MESO, SARC, and UVM (all $p<0.05$, Figure 4L-R). RUNX3 had a protective role in BRCA and ESCA (all $p<0.05$, Figure 4S-T) but a detrimental role in LGG (all $p<0.05$, Figure 4U).

In addition, we analyzed the relationship of the *RUNX* gene family expression and DSS in pan-cancer. The results suggested that increased expression of RUNX1 was associated with poor DSS in GBM, LGG, KIRC, OV, MESO, and UVM, whereas, increased RUNX1 expression predicted good DSS in SKCM, THYM, and BRCA (all $p<0.05$, Figure 5A-I). RUNX2 had a detrimental role in KICH, KIRC, LGG, MESO, and UVM (all $p<0.05$, Figure 5J-N). RUNX3 had a detrimental role in LGG ($p<0.05$, Figure 5O).

The same method is used to analyze DFI in 33 TCGA tumors. RUNX1 had a protective role in BRCA ($p<0.05$, Figure 6A). On the other hand, RUNX1 had a detrimental role in PAAD and CESC (all $p<0.05$, Figure 6B-C). The high expression of RUNX2 was a protective factor in LIHC, PARD, and TGCT (all $p<0.05$, Figure 6D-F), but was all a risk factor in the LUAD (all $p<0.05$, Figure 6G). RUNX3 had a protective role in LIHC and UCS ($p<0.05$, Figure 6H-I).

Finally, we also analyzed the PFI in 33 TCGA tumors. RUNX1 expression had a detrimental role in CESC, COAD, GBM, KIRC, LGG, and UVM (all $p<0.05$, Figure 7A-F), but was all a protective role in the BRCA and SKCM (all $p<0.05$, Figure 7G-H). The high expression of RUNX2 was a protective factor in LIHC (all $p<0.05$, Figure 7I), but was all a risk factor in the KICH, LGG, and UVM (all $p<0.05$, Figure 7J-L). RUNX3 had a detrimental role in GBM, LGG, PARD, and THYM ($p<0.05$, Figure 7M-P).

We also explored the relationship of *RUNX* gene family expression and clinicopathologic stage. Our results demonstrated that the *RUNX* gene family expression levels in several tumor tissues were significantly different in different clinical stages. With the increase of tumor grade, the expression of RUNX1 increased in the UVM, and the expression of RUNX2 increased in the STAD, ESCA and KICH. In contrast, as the tumor grade increased, the expression of RUNX1 decreased in BLCA and BRCA, and the expression of RUNX3 decreased in TGCT (Supplementary Figure 1).

3.3 Correlation of RUNX family expression with tumor microenvironment and tumor stemness

The tumor microenvironment plays a crucial part in the initiation, progression metastasis, and drug resistance of cancer[18, 19]. In this study, we explored the association between the *RUNX* gene family and the tumor microenvironment by using the ESTIMATE algorithm to calculate immune and stromal scores and tumor purity in diverse cancer types from the TCGA database. After a series of analyses, we observed a positive pan-cancer association between the *RUNX* gene family and ESTIMATE scores (Figure 8A-C). This suggests that the three members of the *RUNX* gene family show similar role in the tumor microenvironment.

In addition, we assessed the pan-cancer correlations between the *RUNX* gene family and tumor stemness. Using the TCGA tumor stemness database, RNAss and DNAss were analyzed. Our results showed that the *RUNX* gene family had a negative correlation with RNAss (Figure 8D). By contrast, it had a positive correlation with DNAss in CHOL, KIRP, LGG, MESO, THCA and UVM (Figure 8E).

Furthermore, we analyzed the correlation between TMB or MSI and the *RUNX* gene family expression in different types of cancers. Of the three family members, we found that RUNX1 expression was significantly associated with TMB in MESO, LUSC, LIHC, LGG, LAML, KIRP, HNSC, ESCA, CESC, BRCA, and BLCA (Supplementary Figure 2A). We found that gene expression was significantly correlated with MSI in LUSC, LUAD, KIRC, HNSC, DLBC, and CHOL (Supplementary Figure 2B). A significant correlation was found between RUNX2 expression and TMB in various cancers, such as LIHC, KIRP, KICH, HNSC, ESCA, CHOL, and BRCA (Supplementary Figure 2C), while, RUNX2 expression was correlated with MSI in LIHC, HNSC, DLBC, and COAD (Supplementary Figure 2D). We found that RUNX3 expression was significantly associated with TMB in PAAD, LUAD, LIHC, LGG, KIRP, ESCA, and BRCA (Supplementary Figure 2E). We also found that gene expression was significantly correlated with MSI in OV, LGG, KIRP, ESCA, DLBC, COAD, and BRCA (Supplementary Figure 2F).

3.4 Correlation of RUNX family expression with tumor immune subtype and immune checkpoints

Tumor-infiltrating immune cells are crucial components of the tumor microenvironment and promote the immune escape of cancer. To clarify the molecular significance of the *RUNX* gene family in tumor-infiltrating immune cells, we analyzed the potential relationship between expression of the RUNX family and tumor immune subtypes. The members of the RUNX family were all related to immune subtypes on a pan-cancer basis. RUNX1 had higher expression in C1, C2, C3, C4, and C6. Higher levels of RUNX2 were associated with C1, C2, and C6. RUNX3 showed higher expression in C1, C2, C3, and C6 (Figure 9A). We also analyzed the correlations between *RUNX* gene family expression and 47 common immune checkpoint genes, across all cancer types in the TCGA database. As shown in Figure 9B, in most cancers, except CESC, CHOL, MESO, LAML, and UCS, RUNX1 expression was significantly correlated with immunoinhibitory genes. Additionally, except CESC, MESO, and UCS, RUNX2 expression was significantly correlated with immunostimulatory genes (Figure 9C). RUNX3 expression was significantly correlated

with immunostimulatory genes, except UCS (Figure 9D). This suggested a potential synergy of *RUNX* gene family with known immune checkpoints.

3.5 Genetic alteration analysis of *RUNX* gene family

Using the cBioPortal database (10967 samples from 32 studies), we analyzed the genetic alterations of the *RUNX* gene family in different cancer types. Our results show that LAML had a relatively high mutation level, with RUNX1 alterations exceeding 13% with “mutation” as the primary type; the hot spot mutation of RUNX1 was D96Gfs*15/Gfs*11/Mfs*10 in the Runt domain, which occurred in nine cancers (LAML and BRCA) in nine patients and resulted in a truncated protein (Figure 10A-B, G). The highest alteration frequency of RUNX2 (>6%) appeared for patients with esophageal adenocarcinoma with primary type “amplification” (Figure 10C-D). The hot spot mutation S31Pfs*9 of RUNX2 occurred in five cancers (STAD and COAD) in five patients and also encoded a truncated protein (Figure 10H). Compared with RUNX1 and RUNX2, the genetic alteration level of RUNX3 was relatively low. Specifically, SKCM patients had the highest alteration frequency of RUNX3, with “mutation” as the primary type (Figure 10E-F, I).

3.6 Drug response analysis of *RUNX* gene family

In order to investigate the potential relationship between the *RUNX* gene family and drug response in various human cancer types, we performed a correlation analysis to screen out the association between *RUNX* gene family and drug response from the CellMiner database. In this study, Z-score was used to measure drug response. Specifically, RUNX1 expression was positively associated with drug response to batracylin, tricinbine phosphate, nelarabine, chelerythrine, irinotecan, bendamustine, clofarabine, and asparaginase (Figure 11B-D, F-H, N, O). RUNX2 expression was positively associated with response to staurosporine, bleomycin, and dasatinib (Figure 11L, M, P). RUNX3 expression was positively associated with hypothemycin, selumetinib, PD-98059, dabrafenib, and dasatinib (Figure 11A, E, I-K).

3.7 Functional enrichment analysis of the *RUNX* gene family

To perform a comprehensive functional and pathway analysis of the *RUNX* gene family, we used GeneMANIA to screen out other genes or transcription factors associated with the *RUNX* gene family. The results showed that several transcription factors (Figure 12) were potential targets of RUNX family members. In addition, according to the analysis, RUNX members and related transcription factors were involved in the following pathways or functions: chromatin, regulatory region DNA binding, regulatory region nucleic acid binding, histone deacetylase binding, transcriptional repressor complex, and activating transcription factor binding.

3.7 *RUNX* gene family in UVM

We also studied the relationship between the expression level of the *RUNX* gene family and the ESTIMATE score and immune subtype. The expression of *RUNX* gene family members were all related to immune subtypes in UVM. Notably, only C3, C4, and C5 immune subtypes were observed in the *RUNX* gene family (Figure 13A). We also conducted a correlation analysis, which showed that expression of *RUNX2* was negatively associated with RNAss in UVM. The expression levels of *RUNX1* and *RUNX2* were positively associated with DNAss in UVM. Besides, for all three members of the *RUNX* gene family, expression levels were positively associated with stromal score, immune score, and ESTIMATE score (Figure 13B). Using the data from HPA cohort, we also analyzed the differential protein expression of *RUNX* family. Our result shown that the aberrant expression of *RUNX1* was detected in metastatic melanoma tissues, when compared normal tissues. However, there was no significantly expression different of *RUNX2* and *RUNX3* between metastatic melanoma tissues and normal tissues (Figure 13C).

4 Discussion

In recent years, several studies have shown that the *RUNX* gene family is closely related to the processes of tumor growth, invasion, metastasis, and drug response[20]. However, there is no pan-cancer evidence of the relationship between *RUNX* gene family members and various tumors. Our study, for the first time, used TCGA, Oncomine, and cBioPortal to conduct a pan-cancer analysis of the *RUNX* gene family (*RUNX1*, *RUNX2*, and *RUNX3*) in 33 different human cancer types and matched normal tissues. In brief, all three members of the *RUNX* gene family showed significant aberrant expression in various types of cancer compared with matched normal tissues. *RUNX1* showed higher expression in 14 types of cancer and low expression in one type. *RUNX2* had higher expression in 12 types of cancer and low expression in one type. *RUNX3* was overexpressed in nine types of cancer and showed low expression in five types. These results suggest that members of the *RUNX* gene family are potential tumor biomarkers. In addition, we observed significant heterogeneity in the gene expression of the *RUNX* gene family across different tumor types in TCGA. Taken together, these contradictory pan-cancer gene expression levels could be attributed to the functional complexity of the *RUNX* gene family and the heterogeneity of tumors. However, additional experiments are required to further evaluate the potential role of the *RUNX* gene family.

The current study also assessed the association between the *RUNX* gene family and patient OS in the 33 different types of cancer. According to our results, the prognostic roles of members of the *RUNX* gene family varied among different cancer types. *RUNX1* and *RUNX2* were significantly associated with poor prognosis in KIRC, LGG, MESO, and UVM. In addition, *RUNX3* had a detrimental role in LGG. On the other hand, *RUNX1* and *RUNX3* were significantly associated with better prognosis in BRCA and ESCA, and *RUNX1* and *RUNX2* were significantly associated with improved survival in SKCM. However, several studies have reported an association of high expression of *RUNX3* with poor prognosis in gastric cancer[21, 22]. These contradictory results and inconsistent data for *RUNX3* are due to the use of different data collection methods and the different roles of *RUNX3* biological characteristics. More

molecular experimental and clinical research is needed to investigate whether high expression of RUNX3 has an essential role in gastric cancer. We also found that the expression of the *RUNX* gene family were significantly correlated with the clinicopathologic stage in various tumors. In summary, these results suggest that members of the *RUNX* gene family are potential prognostic markers for various cancers.

Furthermore, we explored the relationships between the *RUNX* gene family and tumor microenvironment and tumor stemness. Several studies have shown that the tumor microenvironment promotes tumor metastasis and tumorigenesis[23–25]. Based on the ESTIMATE algorithm, the *RUNX* gene family was correlated with different tumor-stromal and immune scores, and tumor purity. These findings have been partially verified by previous studies. RUNX1 is clearly associated with mesenchymal stem cell proliferation and differentiation into myofibroblasts[26]. RUNX3/TGF- β 1 were also related to the cancer-associated fibroblasts in the tumor microenvironment, which can increase promote tumor progression and lead to poor prognosis in colorectal cancer[27]. Activation of RUNX2 in prostate cancer also promotes tumor microenvironment remodeling, which ultimately increases tumorigenesis and disease progression[28]. These findings indicate that the *RUNX* gene family could have synergistic effects on immune functions in cancers. Mechanistic studies will be needed in the future to validate the relationship between *RUNX* gene family expression and the tumor microenvironment at the cellular and molecular levels. In addition, we analyzed the correlations between these genes and tumor stemness scores. Our results showed that the *RUNX* gene family has a clear relationship with RNAss and DNAss. Previous studies have indicated that higher RNAss and DNAss scores were related to tumor dedifferentiation and tumor metastasis, indicating potential drug targets for tumor chemotherapy[29, 30].

Previous studies have reported that members of the *RUNX* gene family have crucial roles in immune reaction and immune cell infiltration. For example, RUNX3 was shown to promote CD8 + T cell recruitment in the LUAD immune microenvironment[31]. To better understand the association between the *RUNX* gene family and immune cell infiltration, we investigated the relationships between the RUNX family and immune subtypes. Previous work showed that patients with C4 and C6 immune subtypes had poor prognosis[32]. We found that all RUNX family members were related to more aggressive immune subtypes, including C1, C2, and C6. In UVM, the members of the *RUNX* gene family were more highly expressed in C3, C4, and C5. Previous results have indicated that C4 was correlated with macrophages[33]. Expression of RUNX3 can also promote monocyte–macrophage differentiation in metastatic melanoma[34]. These findings could help clinicians to identify patients who respond to such immunotherapies. However, the relationships between *RUNX* gene family members and immune infiltration need more extensive and in-depth research to fully explain them.

Another important aspect of this study was the potential correlation between the *RUNX* gene family and drug response according to the CellMiner database. CellMiner is a database and query tool designed for the cancer research community, to facilitate integration and study of molecular and pharmacological data for the NCI-60 cancerous cell lines. Depletion of RUNX2 significantly increases gemcitabine sensitivity of both p53-null and p53-mutated pancreatic cancer cells[35]. Overexpression of RUNX3 in gastric cancer cells can sensitize cells to chemotherapeutic drugs, whereas its downregulation can

facilitate multidrug resistance[36]. Undoubtedly, extensive research is needed to provide new approaches to anticancer drug development. Overall, we found that gene expression levels of the *RUNX* gene family were related to drug response, indicating that members of this family may be promising molecular targets for the treatment of cancer patients.

This study had some limitations. First, it consisted of a bioinformatic analysis to illustrate *RUNX* gene family profiles, including expression, prognostic value, and mutation status in human cancers; there were no *in vivo* or *in vitro* experiments to validate these results. Therefore, future studies should focus on the mechanism of the *RUNX* gene family in different types of cancer. Second, although immune subtypes and ESTIMATE score were found to be significantly correlated with the *RUNX* gene family in UVM, the cellular and molecular mechanisms underlying these correlations require further clarification.

In summary, we obtained a comprehensive and systematic pan-cancer description of the *RUNX* gene family. Our results indicate that the *RUNX* gene family is associated with levels of immune infiltration, poor prognosis, and drug response in various types of cancer. In addition, these findings highlight the potential use of members of the *RUNX* gene family as biomarkers for cancer progression and prognosis, and as potential treatment targets in various cancer types[37–40].

Abbreviations

RUNX: Runt-related transcription factors

TCGA: the Cancer Genome Atlas

HPA: the human protein atlas

ACC: adrenocortical carcinoma

BLCA: bladder urothelial carcinoma

BRCA: breast cancer

CHOL: cholangiocarcinoma

COAD: colon adenocarcinoma

ESCA: esophageal carcinoma

GBM: glioblastoma multiforme

HNSC: head and neck squamous 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

READ: prostate adenocarcinoma; rectum adenocarcinoma

SARC: sarcoma

SKCM: skin cutaneous melanoma

STAD: stomach adenocarcinoma

THCA: thyroid carcinoma

THYM: thymoma

UCEC: uterine corpus endometrial carcinoma

UVM: uveal melanoma

OS: overall survival

DSS: disease-specific survival

PFI: progression-free interval

DFI: disease-free interval

HR: hazard ratios

95% CI: 95% confidence intervals

TGFb: tumor growth factor b

RNAss: RNA stemness scores

DNAss: DNA stemness scores

TMB: Tumor mutation burden

MSI: microsatellite instability

NCI: National Cancer Institute

Declarations

Data Availability Statement

Publicly available datasets were analyzed in this study. This data can be found here: TCGA database (<http://cancergenome.nih.gov>),UCSC Xena (<https://xenabrowser.net/>), Oncomine database (www.oncomine.org), the National Cancer Institute (NCI)-60 database via the CellMiner database (<https://discover.nci.nih.gov/cellminer/home.do>), and GeneMANIA (<http://www.genemania.org>).

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Author Contributions

Han Zhao, Yun Chen: Contributed to conception, design, data acquisition and interpretation, drafted and critically revised the manuscript.

Peijun Shen: Contributed to data acquisition and interpretation and critically revised the manuscript.

Lan Gong: Contributed to design and critically revised the manuscript.

All authors gave their final approval and agree to be accountable for all aspects of the work.

Funding

This study was supported by the National Natural Science Foundation of China (Grant nos. 82070924)

Acknowledgments

None

Ethics declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Figures

Figure 1

Figure 1

Expression levels of RUNX gene family in different types of human cancers. (A) Numbers of datasets with statistically significant increased (red) or decreased (blue) mRNA expression of RUNX from Oncomine. (B) RUNX1, (C) RUNX2, and (D) RUNX3 gene expression levels in different cancer types (red) and normal tissue (blue). * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$. Names in red indicate high expression and those in blue indicate low expression of the corresponding RUNX family gene.

Figure 2

Figure 2

Expression levels and correlations of RUNX family genes in different cancer types from TCGA. (A) Boxplot of RUNX family gene expression across various cancer types. (B) Heatmap of RUNX family gene expression levels in different cancer types and normal tissues from TCGA data. (C) Positive (blue) and negative (red) correlations between RUNX family genes.

Figure 3

Figure 3

Correlation analysis of RUNX family gene expression and patient survival by the Cox method in different cancer types. Different colored lines represent the risk values of different genes in various cancers; HR<1 represents low risk and HR>1 represents high risk. Univariate Cox proportional hazard regression models were used for the association tests.

Figure 4

Figure 4

Kaplan–Meier survival curves comparing pan-cancer high and low expression of RUNX family genes. OS survival curves for RUNX1 in different cancers: (A) BRCA, (B) ESCA, (C) SKCM, (D) KIRC, (E) KIRP, (F) LGG, (G) MESO, (H) OV, (I) UVM. OS survival curves for RUNX2 in different cancers: (J) PCPG, (K) SKCM, (L) BLCA, (M) KICH, (N) KIRC, (O) LGG, (P) MESO, (Q) SARC. OS survival curves for RUNX3 in different cancers: (R) UVM, (S) BRCA, (T) ESCA, (U) LGG.

Figure 5

Figure 5

Kaplan–Meier survival curves comparing pan-cancer high and low expression of RUNX family genes. DSS survival curves for RUNX1 in different cancers: (A) GBM, (B) LGG, (C) KIRC, (D) OV, (E) MESO, (F) UVM, (G) SKCM, (H) THYM, (I) BRCA. DSS survival curves for RUNX2 in different cancers: (J) KICH, (K) KIRC, (L) LGG, (M) MESO, (N) UVM. DSS survival curves for RUNX3 in different cancers: (O) LGG.

Figure 6

Figure 6

Kaplan–Meier survival curves comparing pan-cancer high and low expression of RUNX family genes. DFI survival curves for RUNX1 in different cancers: (A) BRCA, (B) PAAD, (C) CESC. DFI survival curves for RUNX2 in different cancers: (D) LIHC, (E) PARD, (F) TGCT, (G) LUAD. DFI survival curves for RUNX3 in different cancers: (H) LIHC, (I) UCS.

Figure 7

Figure 7

Kaplan–Meier survival curves comparing pan-cancer high and low expression of RUNX family genes. PFI survival curves for RUNX1 in different cancers: (A) CESC, (B) COAD, (C) GBM, (D) KIRC, (E) LGG, (F) UVM, (G) BRCA, (H) SKCM. PFI survival curves for RUNX2 in different cancers: (I) LIHC, (J) KICH, (K) LGG, (L) UVM. PFI survival curves for RUNX3 in different cancers: (M) GBM, (N) LGG, (O) PARD, (P) THYM.

Figure 8

Figure 8

Correlation matrix plots of RUNX family gene expression with tumor microenvironment and stemness scores in 33 different cancer types. (A-C) RUNX family gene expression was associated with ESTIMATE, immune, and stromal scores in different cancers. (D, E) RUNX family gene expression was associated with RNAss and DNAss in different cancers. Spearman's correlation was used for testing. Red dots indicate a positive correlation between gene expression and immune/stromal score, and blue dots

indicate a negative correlation. The size of each dot represents the absolute value of the correlation coefficient.

Figure 9

Figure 9

Association of RUNX family gene expression with immune infiltrate subtypes and immune checkpoints. (A) Association of RUNX family gene expression with immune infiltrate subtypes across all types of cancer ($p < 0.001$) tested with ANOVA. X-axis represents immune subtype; Y-axis represents gene

expression. (B-D) The correlations between RUNX1 (B), RUNX2 (C), and RUNX3 (D) and confirmed immune checkpoints in multiple cancers (*p < 0.05, **p < 0.01, ***p < 0.001).

Figure 10

RUNX family gene mutation landscape. (A) RUNX1, (C) RUNX2, and (E) RUNX3 mutation frequency in multiple TCGA pan-cancer studies according to the cBioPortal database. General mutation count for (B)

RUNX1, (D) RUNX2, and (F) RUNX3 in various TCGA cancer types from the cBioPortal database. Mutation diagram of (G) RUNX1, (H) RUNX2, and (I) RUNX3 in different cancer types across protein domains.

Figure 11

Figure 11

Drug sensitivity analysis of RUNX family gene. RUNX1 expression was positively associated with sensitivity to (B) batracylin, (C) triciribine phosphate, (D) nelarabine, (F) chelerythrine, (G) irinotecan, (H) bendamustine, (N) clofarabine, and (O) asparaginase; RUNX2 expression was positively related to

sensitivity to (L) staurosporine, (M) bleomycin, and (P) dasatinib; and RUNX3 expression was positively associated with sensitivity to (A) hypothemycin, (E) selumetinib, (I) PD-98059, and (J) dabrafenib and negatively related to sensitivity to (K) dasatinib.

Figure 12

Figure 12

Comprehensive functions and pathways analysis for RUNX gene family by GeneMANIA. Different line colors indicate different networks and functions.

Figure 13

Figure 13

Correlation analysis between RUNX gene family and immune subtype and tumor microenvironment in UVM. (A) Correlations between RUNX gene family and immune infiltration subtypes in UVM. (B) Correlations between RUNX gene family and tumor stemness score and ESTIMATE score. R is the correlation value. (C) Representative immunohistochemical staining of RUNX1, RUNX2, and RUNX3 protein in metastatic melanoma tissues and normal tissues.

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