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An Integrative Pan-Cancer Analysis Revealing CHRM1 Is a Potential Immunological and Prognostic Biomarker

Zhengwei Su[1,2#], Qingming Huang[1,2#], Han Tang[1,2#], Chengjie Ban[1,2], Huadong Xie[1,3], Tianling Liao[1,4], Kangji Liao[1], Zhi Cheng[1,3] and Xian-lin Yi[1*]

[1]Department of Urology, Maternal and Child Health Hospital of Hubei Province, Tongji Medical College, Huazhong University of Science and Technology, China

[2]Department of Urology, CancerHospital of Guangxi Medical University, China

[3]Department of Urology, The Second Affiliated Hospital of Guangxi Medical University, China

[4]Department of Traditional Chinese Medicine, The First Affiliated Hospital of Guangxi Medical University, China

Contributions: (I) Conception and design: Zhengwei Su, Qingming Huang, Han Tang; (II) Administrative support: Xian-lin Yi, Yong Tang; (III) Collection and assembly of data: Chengjie Ban, Huadong Xie, Tianling Liao, Kangji Liao, Zhi Cheng; (IV) Data analysis and interpretation: Zhengwei Su, Qingming Huang, Han Tang; (V) Manuscript writing: All authors; (VI) Final approval of manuscript: All authors.

#These authors contributed equally to this work

[*]**Corresponding author:** Xian-lin Yi, Maternal and Child Health Hospital of Hubei Province, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China, Tel: +86 15296521231

Abstract

Objective: To investigate the expression level, prognostic value, immunoinfiltration and GSEA enrichment analysis of CHRM1 gene in pan-cancer, and to provide a new target for tumor treatment and prognosis prediction.

Methods: UCSC Xena was used to analyze CHRM1's differential expression in pan-cancer. Cox regression and Kaplan-Meier were used to assess CHRM1's prognostic value. Spearman and Wilcoxon tests were conducted to explore CHRM1's correlation with TMB, MSI, TME, and immune cell infiltration. GSEA and drug sensitivity analysis were conducted, and R packages were used to create gene co-

expression heatmap and enrichment pathway map.

Result: CHRM1 is downregulated in various tumors vs. normal tissues and correlates with poor patient prognosis. CHRM1 expression is closely linked to TMB, MSI, TME, and immune cell infiltration across tumors. The expression of CHRM1-related genes can impact tumor cell signaling and metabolism, promoting tumor development.

Conclusion: CHRM1 is an important tumor prognosis-related gene that regulates the composition of the TME and is significantly related to a variety of immunotherapy targets. CHRM1 may be a biomarker for finding new immunotherapeutic targets and new anti-tumor drugs and predicting their efficacy.

Keywords: CHRM1; Pan-cancer analysis; TME; Gene coexpression; GSEA

Introduction

Cancer is a major public health problem and the leading cause of death worldwide [1]. There are five subtypes (M1~5) of Muscarinic Acetylcholine Receptors (mAChR), which play different physiological and biological functions in different tissues and cell types. The Cholinergic Receptor Muscarinic 1 (CHRM1) gene is located on human chromosome 11q12.3, which encodes the expression of M1 receptors. M1 is mainly distributed in the nervous system, and its activation can lead to an increase in the calcium concentration in nerve cells, thereby affecting synaptic transmission. Cancer progresses from precancerous lesions to overt cancer, almost doubling nerve density in the process compared to non-tumoral tissue controls (age matched) [2,3]. The peripheral nervous system enables the body to maintain homeostasis by coordinating the molecular, cellular, and organ levels. Similarly, cancer cells must regulate these processes to ensure their survival [4]. The contribution of nerves to the pathogenesis of malignant tumors has become an important part of the tumor microenvironment. In the process of tumorigenesis, cancer not only escapes the body's regulatory mechanisms but also acquires the ability to affect local and systemic homeostasis, and tumor cells can produce cytokines [5], immune mediators [6], neurotransmitters [7,8], etc. Muscarinic receptor activation and downstream signaling have been shown to stimulate cell proliferation in lung cancer [9], breast cancer [10], prostate cancer [11], and colon cancer [12]. Therefore, the activation of muscarinic receptor signaling is likely to play an important role in tumorigenesis and development. However, current research on CHRM1 is limited to a few types of tumors; for example, in a mouse model of prostate cancer, cholinergic signals transduced by CHRM1 in the tumor stroma promote tumor invasion [13], and inhibition of pancreatic tumorigenesis by muscarinic signaling is mediated by CHRM1 [14]. At present, the expression pattern and prognostic value of CHRM1 in pan-cancer are still not fully understood. In this study, the expression level and prognostic value of CHRM1 in pan-cancer were analyzed for the first time using a dataset of 33 cancers from the UCSC Xena database. In addition, we explored the relationship between CHRM1 expression and Tumor Mutation Burden (TMB), Microsatellite Instability (MSI), Tumor Microenvironment (TME) and tumor immune cell infiltration. At the same time, we performed immune gene coexpression analysis and Gene Set Enrichment Analysis (GSEA) for CHRM1 and preliminarily explored antitumor drugs related to CHRM1. This study preliminarily reveals the potential and application value of CHRM1 as a pan-cancer prognostic marker and provides a research

basis for the diagnosis and treatment of tumors.

Data and Methods

Data sources

Data were obtained from the UCSC Xena (University of California, Santa Cruz, Xena Public, http://xena.ucsc.edu/) and the corrected HTSeq-FPKM dataset of 33 tumors were downloaded, from which the mRNA expression data of CHRM1 in each sample were extracted, and the survival data of each tumor were also downloaded. We also downloaded mutation data for 33 tumors with somatic mutations (SNPs and small INDELs). Datasets including DFI, DSS, and PFI were downloaded from the curated clinical data pan-cancerAtlas Hub in TCGA Pan-Cancer (PANCAN).

Differential expression of CHRM1 in pan-cancer and different stages

In this study, R software (version 4.3.0) was used to calculate the differential expression of CHRM1 in 33 tumor samples. The "ggboxplot" function in the R package "ggpubr" was used to draw box plots, and the unpaired "Wilcox.test" rank sum test was used to analyze the significance of differences between the normal group and the tumor group. The stage was divided into stage I to stage IV. The differential expression of CHRM1 in different stages was analyzed by the same method, and the difference between different stages was analyzed.

Pan-cancer prognostic value of CHRM1

According to the median value of CHRM1 expression, tumors were divided into high and low-expression groups. The Kaplan–Meier method was used to analyze the difference between the two groups, and the R package "survival" was used to draw the survival curve and risk table. Univariate Cox analysis was used to analyze the relationship between gene expression and survival time and survival status, and the R package "forestplot" was used to draw the forest map for display. The relationship between CHRM1 expression and the Overall Survival (OS), Disease-Specific Survival (DSS), Disease-Free Interval (DFI) and Progression-Free Interval (PFI) of patients was analyzed.

Correlation between CHRM1 expression and TMB, MSI, and TME

TMB counts the number of mutations per million DNA base pairs, and MSI quantizes the spontaneous loss or gain of nucleotides in short tandem repeat DNA segments. In this study, the correlation between CHRM1 expression and TMB and MSI was analyzed. R software was used for statistical analysis, "Spearman" was used to test the two groups of data, the "radarchart" function in the R package "fmsb" was used to draw the radarchart, and a p value < 0.05 was considered statistically significant. The relationship between CHRM1 expression and the content of stromal cells and immune cells in the TME was also analyzed. The R packages "ggplot2", "ggpubr" and "ggExtra" were used to draw graphs, and "Spearman" was used to test the two sets of data.

Immune infiltration analysis and gene coexpression

We analyzed the correlation between 22 immune cells, such as naive B cells, CD4 T cells, neutrophils, macrophages and CHRM1 expression, in pan-cancer. The R packages "ggplot2", "ggpubr" and "ggExtra" were used to draw graphs, and the correlation between immune cell content and gene expression was tested using "Spearman". We also analyzed the coexpression of CHRM1 with immune genes in pan-cancer and performed correlation tests using the "cor.test". The R packages "reshape2", "RColorBrewer", and "pheatmap" were used to draw

the heatmap of gene coexpression.

Gene set enrichment analysis (GSEA)

In this study, we analyzed the pathways or functions through which the expression of target genes affects tumorigenesis. With the median value of target gene expression divided into two groups of high and low expression, the KEGG database "c2. Cp. KEGG. V2023.1. Hs. Symbols. gmt" as a gene-to-gene mapping information reference. The R packages "org.Hs.eg.db", "clusterProfiler" and "enrichplot" were used to draw the enrichment analysis graph of KEGG pathways for the CHRM1-related gene set, and a P value < 0.05 was considered statistically significant.

Correlation analysis of drug sensitivity

The present study analyzed sensitivity to antitumor drugs in relation to CHRM1 expression. We downloaded the RNA-seq dataset and the DTP NCI-60 dataset from the CellMiner (https://discover.nci.nih.gov/cellminer/home.do) database. We filtered the drug sensitivity data, only analyzed the FDA certification data and clinical trial certification data, used the R packages "ggplot2" and "ggpubr" to plot the drug sensitivity of gene and visualized the top 16 antitumor drugs with p value ranking.

Results

CHRM1 expression in pan-cancer and different stages

Analysis of CHRM1 expression across cancers based on mRNA expression data from 33 tumors showed that CHRM1 expression is significantly lower than that in normal tissues in 14 types of cancer, including Bladder Urothelial Carcinoma (BLCA), Breast Invasive Carcinoma (BRCA), Colon Adenocarcinoma (COAD), Esophageal Carcinoma (ESCA), Glioblastoma Multiforme (GBM), Head and Neck Squamous Cell Carcinoma (HNSC), kidney renal clear cell carcinoma (KIRC), Kidney Renal Papillary cell Carcinoma (KIRP), Lung Adenocarcinoma (LUAD), Lung Squamous Cell Carcinoma (LUSC), Prostate Adenocarcinoma (PRAD), Rectum Adenocarcinoma (READ), Stomach Adenocarcinoma (STAD), and Thyroid Carcinoma (THCA) ($P<0.05$). CHRM1 expression was significantly higher in Cholangiocarcinoma (CHOL) and Kidney Chromophobe (KICH) than in normal tissues ($P < 0.05$) **(Figure 1)**. To explore the expression of CHRM1 in different stages of cancer, we analyzed the difference in the expression of CHRM1 between the pan-cancer stage (I, II, III and IV). The results showed that CHRM1 expression was significantly different in KICH, KIRP, LUAD, LUSC, Skin Cutaneous Melanoma (SKCM), Testicular Germ Cell Tumors (TGCT) and THCA tumors at different stages ($p<0.05$) **(Figure 2A-G)**.

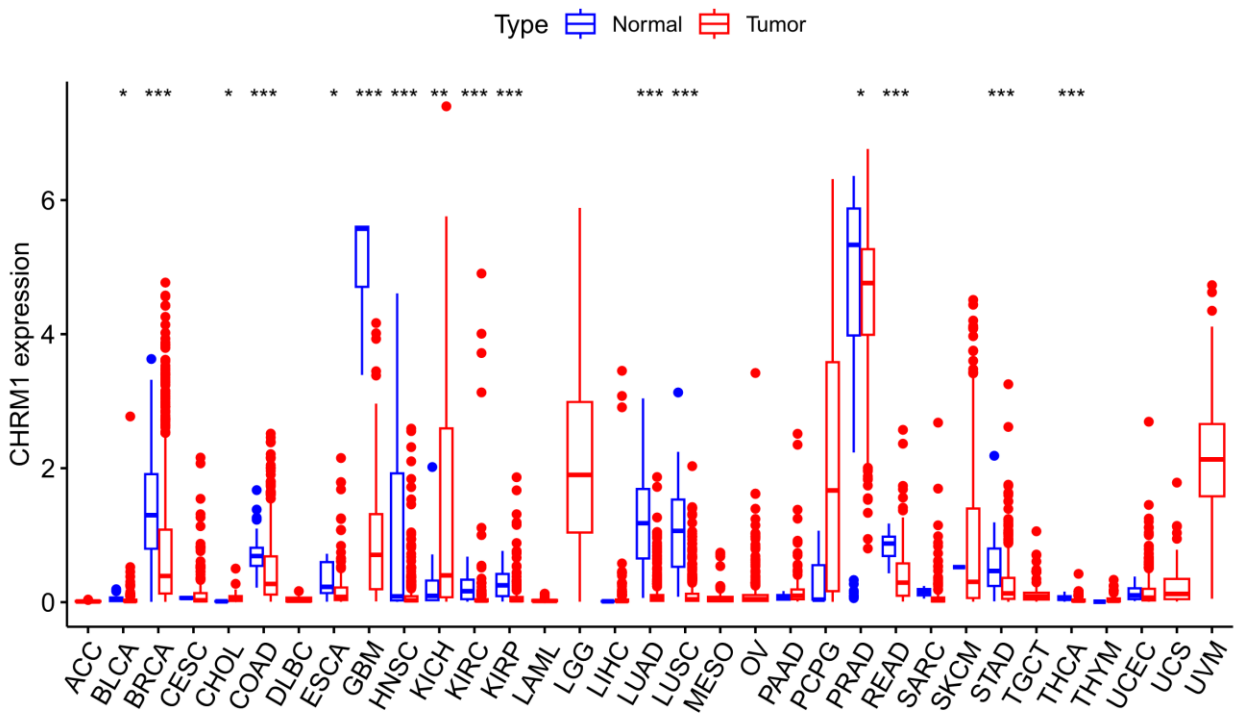


Figure 1: The mRNA expression of CHRM1 in pan-cancer. Compared with the normal group, CHRM1 expression levels in BLCA, BRCA, COAD, ESCA, GBM, HNSC, KIRC, KIRP, LUAD, LUSC, PRAD, READ, STAD and THCA were significantly lower, while in CHOL, KICH increased significantly. (* P＜0. 05,**P＜0. 01,***P＜0. 001).

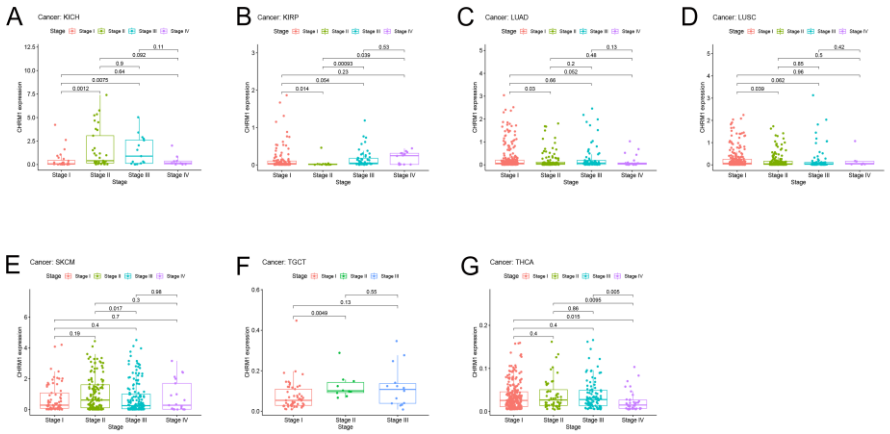


Figure 2: Differential expression of CHRM1 in pan-cancer at different stages. CHRM1 expression was significantly associated with different stages in KICH, KIRP, LUAD, LUSC, SKCM, TGCT, and THCA. (p-value < 0.05).

Pan-cancer prognostic value of CHRM1

We used Kaplan–Meier survival analysis and Cox analysis to explore the prognostic value of CHRM1 in pan-cancer to clarify the prognosis of patients in terms of OS, DSS, DFI and PFI. The results of the forest plot of univariate Cox regression analysis showed that high CHRM1 expression was a protective factor for HNSC, brain Lower Grade Glioma (LGG), PRAD, and LUAD but a risk factor in BRCA **(Figure 3A-D)**. The results of Kaplan–Meier survival analysis showed that low CHRM1 expression in LGG and LUAD was associated with poor prognosis in terms of OS (P<0.05) **(Figure 3E-F)**. The DSS results showed that low CHRM1 expression was associated with worse prognosis in terms of LGG and PRAD, but the opposite was observed for BRCA, KIRP, and SKCM (P<0.05) **(Figure 3G-K)**. In the DFI results, CHRM1 was associated with a poor prognosis in the LUAD, LGG, and Pheochromocytoma and Paraganglioma (PCPG) low-expression groups but a better prognosis in the BLCA low-expression group (P<0.05) **(Figure 4A-D)**. The PFI results showed that low CHRM1 expression was associated with a worse patient outcome in those with LGG and PRAD and a better patient outcome in those with lymphoid neoplasm Diffuse Large B-cell lymphoma (DLBC) and KICH (P<0.05) **(Figure 4E-H)**. These results indicate that CHRM1 expression is closely related to the prognosis of a variety of tumors.

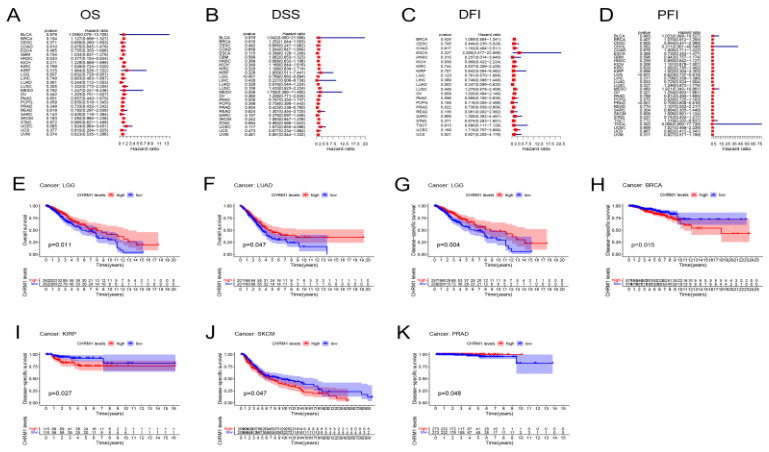


Figure 3: Univariate Cox analysis forest plot and Kaplan–Meier survival analysis curve of OS, DSS, DFS and PFI of CHRM1 in pan-cancer. (A-D). Correlation between CHRM1 expression and OS, DSS, DFI, and PFI; (E-K). Kaplan–Meier analysis showed that the LGG and LUAD low-expression groups had poor prognosis in terms of OS. Low CHRM1 expression was associated with a poor prognosis of LGG and PRAD in terms of DSS, while the opposite was observed in BRCA, KIRP and SKCM. OS: Overall survival; DSS: Disease-specific survival; DFI: disease-free interval; PFI: progression-free interval. (p-value < 0.05).

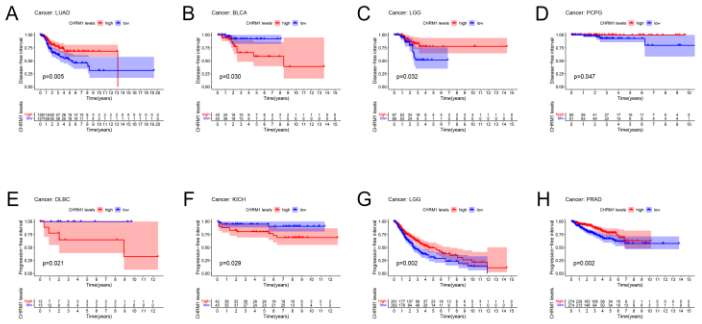


Figure 4: DFI and PFI Kaplan–Meier survival analysis curves of CHRM1 in pan-cancer. (A-D). Kaplan–Meier analysis showed that CHRM1 expression was significantly associated with DFI in patients with LUAD, LGG, PCPG, and BLCA; (E-H). Kaplan–Meier analysis showed that CHRM1 expression was significantly associated with DFI in patients with DLBC, KICH, LGG, and PRAD. (p-value < 0.05).

Correlation between CHRM1 expression and TMB, MSI, and TME

Instead of simply recording the characteristics of cancer cells, the contribution of the "tumor microenvironment" to tumorigenesis must be taken into account in the understanding of tumors [4]. TMB and MSI in the tumor microenvironment are related to antitumor immunotherapy and can be used to predict the efficacy of tumor immunotherapy [15]. The results of TMB and MSI radar plots showed that CHRM1 was positively correlated with TMB in thymoma (THYM), TGCT, mesothelioma (MESO), HNSC, COAD and BRCA ($P < 0.05$), and negatively correlated with TMB in STAD, SKCM, PRAD, LUAD and LGG ($P < 0.05$). For MSI, CHRM1 was positively correlated with uveal melanoma (UVM), TGCT, KICH, COAD, CHOL, and cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC) ($P < 0.05$) and negatively correlated with STAD, sarcoma (SARC), PRAD, and acute myeloid leukemia (LAML) ($P <0.05$) **(Figure 5)**; the TME plays an important role in tumor formation, growth, invasion, metastasis and sensitivity to treatment. Next, we further investigated the correlation between the content of stromal cells and immune cells in the TME and the expression of target genes across cancers. The results showed that the expression of CHRM1 was negatively correlated with the contents of stromal cells and immune cells in GBM, KIRC, LGG and SKCM, with significant differences ($P<0.001$), whereas in TGCT, there was a positive correlation with stromal cell content and a negative correlation with immune cell content **(Figure 6A-J)**. CHRM1 expression was negatively correlated with immune cell content in CESC, ovarian serous cystadenocarcinoma (OV), and THCA, whereas it was positively correlated in BRCA. In PCPG, CHRM1 expression was inversely correlated with stromal cells **(Supplementary Figure 1A-E)**. The above results indicate that CHRM1 may affect antitumor immunity by regulating the composition and immune mechanism of the TME.

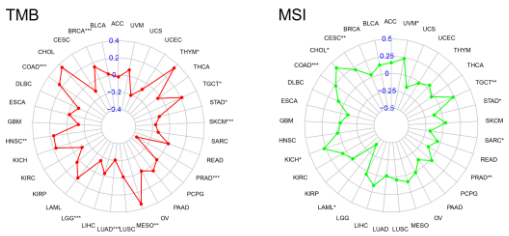


Figure 5: CHRM1 expression was correlated with TMB and MSI in pan-cancer. The results of TMB and MSI radar plots showed that a variety of tumors were significantly correlated with CHRM1 expression. (* P＜0. 05,**P＜0. 01,***P＜0. 001).

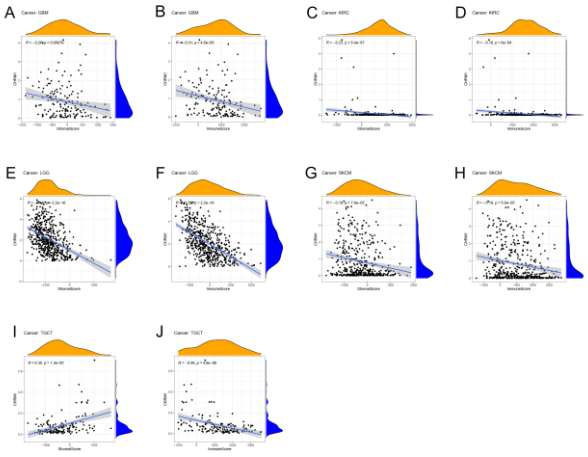
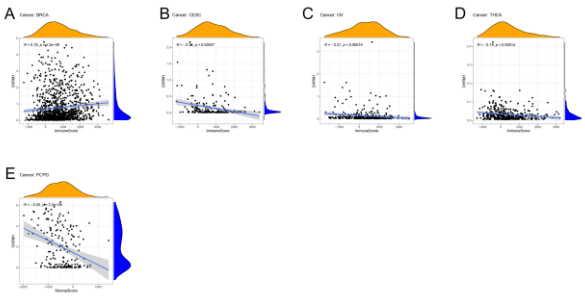


Figure 6: Correlation between the content of stromal cells and immune cells and CHRM1 expression. (A-J). The expression of CHRM1 was negatively correlated with the content of stromal cells and immune cells in GBM, KIRC, LGG and SKCM but positively correlated with the content of stromal cells and negatively correlated with the content of immune cells in TGCT. (p-value < 0.001).



Supplement Figure 1: Association of CHRM1 with stromal and immune cells. (A-E). In CESC, OV and THCA, CHRM1 expression was negatively correlated with immune cells, while BRCA expression was positively correlated. In PCPG, CHRM1 expression was inversely correlated with stromal cells. (p-value < 0.001).

Immune infiltration analysis and gene coexpression

Tumor-infiltrating immune cells are an important part of the TME. B cells, T cells, macrophages, mast cells and neutrophils in the tumor stroma are closely related to the occurrence, development or metastasis of tumors [16]. This study evaluated the association of CHRM1 with immune cell infiltration in 22 types of tumors and showed a significant correlation between CHRM1 expression and immune cell infiltration in 16 types of tumors (P<0.001) **(Supplementary Figure 2A-K)**. CHRM1 expression in BRCA is associated with the infiltration of up to 11 immune cells. In GBM, KIRC, COAD, READ, SKCM, LUAD, TGCT, and STAD, CHRM1 expression was negatively correlated with CD4 memory-activated infiltration of T cells, while it was positively correlated in BRCA **(Figure 7A-I)**. CHRM1 expression was positively correlated with B-cell naive infiltration in BRCA, HNSC, ESCA, LUSC, and STAD, whereas the opposite was observed in TGCT **(Figure 7J-O)**. These results further confirmed the interaction between immune cells and target genes in the TME. To gain more insight into the expression of immune cells in the TME, we next further analyzed the coexpression of CHRM1 with 47 immune genes. The results of the gene coexpression heatmap showed that CHRM1 was negatively correlated with most immune genes in KIRC, LGG, OV, LUAD, PAAD, PCPG, PRAD, SARC, SKCM, TGCT and THCA. Especially in LGG, CHRM1 was negatively correlated with 34 immune genes. These results suggest that high CHRM1 expression may predict poor efficacy of immunotherapy that targets immune genes. However, CHRM1 was positively correlated with most immune genes in a few tumors, such as BLCA, BRCA, COAD, and GBM (P<0.05) **(Figure 8)**. This suggests that CHRM1 may coordinate the activities of these immune genes in different signal transduction pathways, and it is possible to find ideal immunotherapy targets through it. CHRM1 may become a potential biomarker for predicting the response and outcome of immunotherapy in pan-cancer.

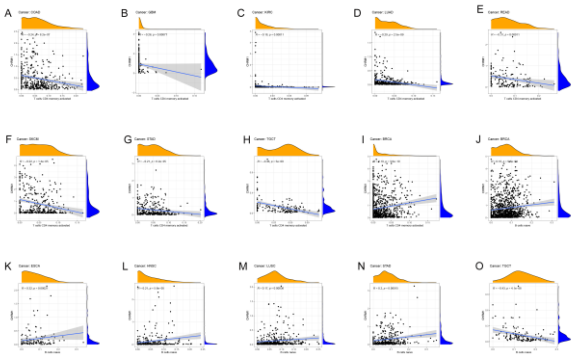


Figure 7: Correlation between CHRM1 and immune cell infiltration in pan-cancer. (A-I). In GBM, KIRC, COAD, READ, SKCM, LUAD, TGCT, and STAD, CHRM1 expression was negatively correlated with T-cell CD4 memory activation but positively correlated with BRCA; (J-O). CHRM1 expression was positively correlated with naive B-cell infiltration in BRCA, HNSC, ESCA, LUSC, and STAD, whereas the opposite was observed in TGCT. (p-value < 0.001).

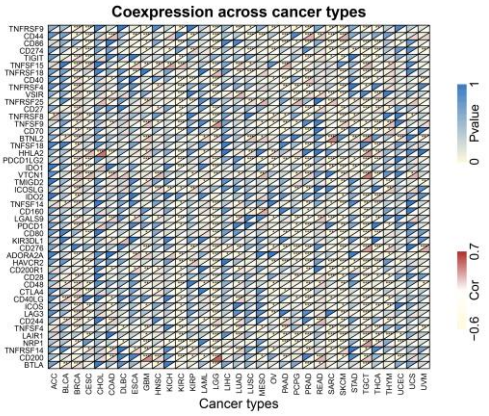
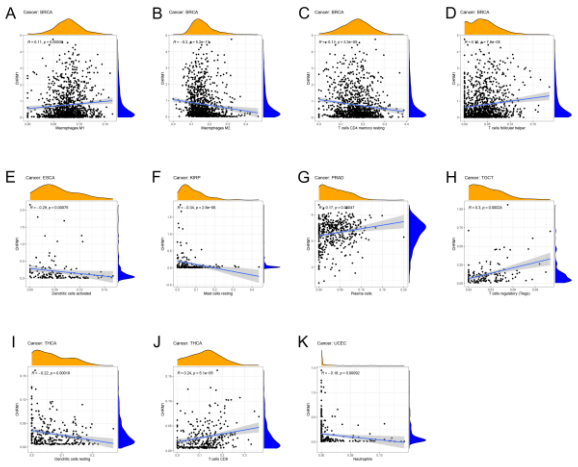


Figure 8: Heat map of CHRM1 co-expression with immune genes. In pan-cancer, CHRM1 expression in most tumors showed a significant correlation with the expression of most immune genes. (* P＜0. 05,**P＜0. 01,***P＜0. 001).



Supplement Figure 2: Correlation of immune cell infiltration. (A-K). In pan-cancer, a variety of immune cells were significantly associated with CHRM1 expression. (p-value < 0.001).

GSEA enrichment analysis

For the study of biological functions, compared with individual genes, the advantage of GSEA is that it uses gene sets, which provide more stable and easily interpretable measures of biological functions [17]. We explored which signaling pathways or metabolic pathways the CHRM1-related gene sets affect the occurrence and development of tumors in pan-cancer and plotted GSEA graphs. The results showed that the expression of gene sets was significantly correlated with enriched pathways in 10 tumors, and most tumors were mainly enriched in neuroactive ligand–receptor interaction pathways, cytochrome P450 metabolism pathways, and immune-related pathways (P<0.05) **(Supplementary Figure 3)**. When the target gene set was highly expressed, the neural conduction and calcium signaling pathways were activated in LGG and GBM, while the porphyrin metabolic pathway was inhibited in LGG but activated in GBM. Fatty acid metabolism, retinol metabolism and cytochrome P450 metabolism are active, while the olfactory pathway is inhibited in LUAD. Primary immunodeficiency, autophagy regulation, NK cell-mediated cytotoxicity, and cytokine-receptor interaction pathways are all active in BRCA (P<0.05) **(Figure 9)**. The above results indicate the important role of CHRM1 in tumor cell signaling and various metabolic pathways.

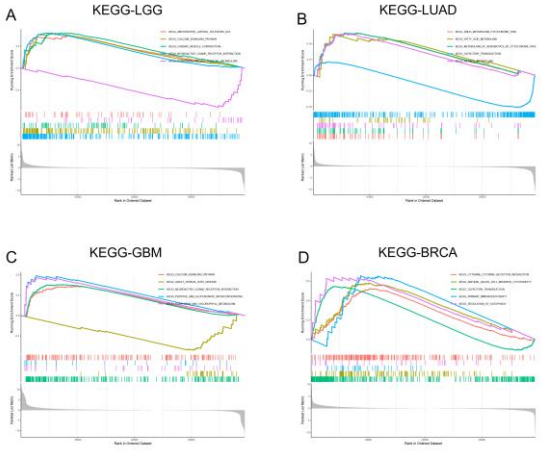
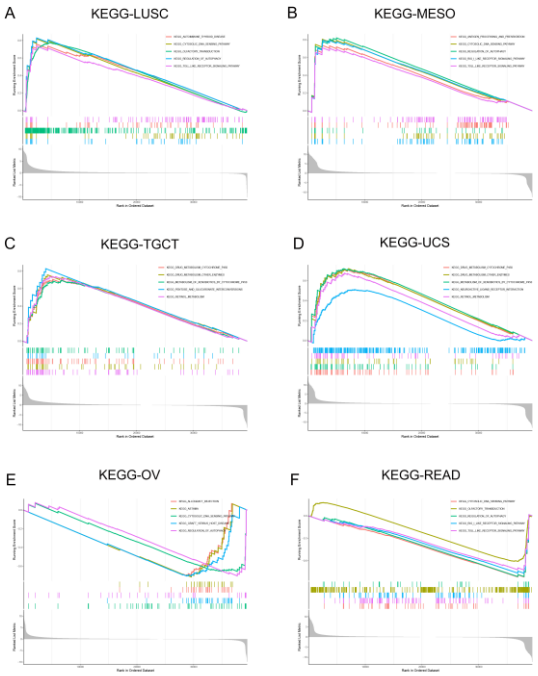


Figure 9: Map of gene set enrichment analysis. The expression of CHRM1-related gene sets was significantly correlated with signaling pathways and metabolic pathways in LGG, GBM, LUAD, and BRCA. (p-value < 0.05).



Supplement Figure 3: Map of gene set enrichment analysis. The expression of CHRM1-related gene sets was significantly correlated with enriched pathways in multiple tumors. (p-value < 0.05)

Correlation analysis of drug sensitivity

Common cancer treatment options include chemotherapy as a first-line treatment and targeted therapy as a second-line treatment. However, drug resistance inevitably becomes a key barrier [18], and the development of next-generation drugs for patients

with drug-resistant tumors is a great challenge and requires significant resources. We initially explored drug susceptibility to CHRM1 gene expression in the CellMiner database. To obtain more convincing results, we only performed statistical analysis on FDA-approved and clinical trial-approved data in the database. The results showed that CHRM1 expression was significantly correlated with 4SC−202 (Cor=0.549, p<0.001), benzimate (Cor=0.407, p=0.001) and 13 other anticancer drugs, indicating that the higher the expression of CHRM1 in cells, the higher the sensitivity to the drug. CHRM1 expression was significantly negatively correlated with three anticancer drugs, including XAV−939 (Cor=−0.324, p=0.014) **(Figure 10)**. CHRM1 expression is significantly correlated with a variety of antitumor drugs, so CHRM1 may be a factor in finding new antitumor drugs and predicting the efficacy of drugs.

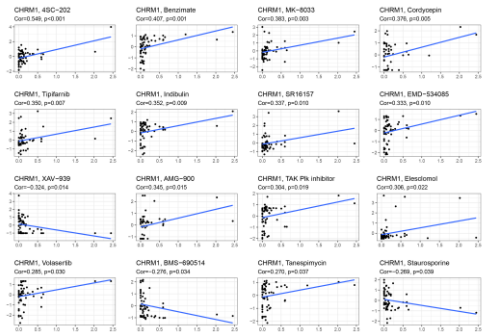


Figure 10: Antineoplastic drug sensitivity associated with CHRM1 expression. Top 16 sensitive antineoplastic agents in the CellMiner database significantly associated with CHRM1 gene expression. (p-value < 0.05)

Discussion

Neoplastic disease is a complex heterogeneous disease. In addition to cancer cells, tumors also contain a series of cells that are recruited to the surroundings of cancer cells. These cells jointly form the "tumor microenvironment" to promote the occurrence and development of tumor cells and gradually allow cancer cells to acquire the characteristics of remodeling energy metabolism and avoiding immune system attack **[4]**. Therefore, the study of tumors is no longer limited to tumor cells, and the in-depth study of the tumor microenvironment is equally important. In tissues, M1 receptors are mainly expressed in the cytoplasm of pyramidal neurons and Purkinje cells. Acetylcholine is used as a neurotransmitter to regulate intracellular and extracellular signal transduction, which is of great significance for cell growth and metabolic processes. As mentioned before, neuromodulation plays an important role in the occurrence and development of tumors, and studies in recent years have shown that information transmission in the nervous system interacts with and affects the TME **[13,14,19,20]**. Therefore, the study of CHRM1 in pan-cancer and the TME allows us to indirectly investigate the correlation between tumors and the nervous system. In this study, we provide the first comprehensive discussion of CHRM1 differential expression in pan-cancer and its correlation with the TME based on RNAseq data

from the UCSC Xene database. We found that CHRM1 was significantly related to the prognosis of LGG, PCPG and other neurocyte-rich tumors and that the OS of LUAD was also significantly different. Studies have shown that 96.9% of LUAD patients have autonomic nerve infiltration (100% of high-risk patients) [21]. Therefore, we hypothesized that CHRM1 may be a good predictor of tumor neural invasion in pan-cancer tissues with significant prognostic differences. This finding has great implications for the use of "denervation" in cancer treatment. Currently, pharmacological inhibition of neural signaling is a promising therapeutic target in anticancer therapy; TMB is related to the prognosis and treatment of tumors, and studies have confirmed that TMB is a determinant of immune-mediated survival of breast cancer [22]. When we explored the effect of CHRM1 on TMB and MSI, we found that a variety of tumors, such as LGG and LUAD, were negatively correlated with CHRM1 in terms of TMB, indicating that the DNA base pair mutation rate of tumors will be reduced when CHRM1 is highly expressed, which is consistent with the better survival prognosis of LGG and LUAD patients when CHRM1 is highly expressed. The number and activity status of tumor-infiltrating lymphocytes are important predictive criteria for cancer survival time [23]. When analyzing the effect of CHRM1 on the TME, we found a significant negative correlation in GBM, indicating that the higher the stromal and immune cell contents were, the lower the expression of the CHRM1 gene. This observation is consistent with our finding that higher CD4 memory-activated T cells in GBM correlated with lower CHRM1 expression in immune infiltration analysis. The goal of immunotherapy is to adjust or enhance the function of the immune system to make it more effective against tumor cells [24]. When studying the coexpression of CHRM1 and immune genes, it was found that several genes, such as CD274 and PDCD1LG2, in GBM were significantly negatively correlated with CHRM1, and Temozolomide (TMZ) attack on GBM cells was achieved by CD274-enhanced transcription [25]. There is a significant negative correlation between PDCD1 and CTLA4 in SKCM, and the cancer of patients with refractory unresectable melanoma is well controlled by treatment with the anti-CTLA4 antibody ipilimumab [26]. Pembrolizumab treatment of SKCM reversed T-cell exhaustion and enhanced antitumor immunity by blocking PD1 [27]. Meanwhile, we found that CHRM1 expression in SKCM was negatively correlated with CD4 memory-activated T cells. The above results indicate that CHRM1 is a bridge mediating immune gene expression and immune cell infiltration in a variety of tumors; therefore, CHRM1 may be a predictor of immunotherapy response in a variety of tumors. Through GSEA, we found that CHRM1 was mainly closely related to the nerve conduction pathway, calcium signaling pathway and immune regulation pathway, which further confirmed that the target gene affected the formation of the TME and played an important role in the occurrence and development of tumors. In the drug sensitivity analysis, a variety of drugs with a significant correlation with CHRM1 expression were found, and CHRM1 may be a factor for predicting efficacy and searching for new antitumor drugs. These results further confirmed the importance of CHRM1 in tumor research throughout the occurrence, development, prognosis and treatment of tumors. However, our study also has some limitations. Although bioinformatics analysis has provided us with some meaningful insights into CHRM1 in pan-

cancer, in vitro or in vivo biological experiments are still needed to verify our findings, and further mechanistic studies will help elucidate and refine the role of CHRM1 at the molecular and cellular levels.

In summary, the data of this study clarified that CHRM1 expression varies in different tumors and is correlated with stage and clinical prognosis. CHRM1 may be a breakthrough in the search for new targets for cancer treatment because it has been shown to be significantly associated with TMB, MSI, TME and immune infiltration in a variety of tumors. In addition, our results provide insights into the essential role of CHRM1 in tumorigenesis, development, and metastasis, providing potential mechanisms by which CHRM1 expression may regulate tumor immunity, metabolic activity, and the TME in cancer. Future prospective studies on CHRM1 expression and the TME may help to provide a definitive answer, and biological experiments in vitro or in vivo will help to clarify the role of CHRM1 in antitumor therapy.

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