The pan-cancer landscape of crosstalk between chemokinesand the tumor immune microenvironment

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Abstract

Background

Chemokines are a subfamily of cytokines known for their ability to promote cell migration, particularly that of immune cells. Chemokines are necessary for immune system function and have attracted considerable attention on account of their roles in regulation of the tumor immune microenvironment.

Methods

Chemokine genes were obtained from the TISIDB database, and we examined the correlation, gene alteration, differential expression, and prognostic value of these genes in 33 tumor types based on Cancer Genome Atlas and Genotype-Tissue Expression data. The chemokine score of each sample was calculated using the “ssGSEA” function of the R package “GSVA.” We also evaluated the correlation between chemokine scores and a tumor immune microenvironment index and assessed the influence of chemokine scores on the response of cancer patients to immune checkpoint inhibitor therapy.

Results

We found that tumor samples with high chemokine scores were immune-activated, and further analysis using three immunotherapy cohorts revealed that patients with high chemokine scores were sensitive to anti-PD-1 therapy.

Conclusions

Our results indicate that chemokines are closely associated with the tumor microenvironment, and consequently, patients with high chemokine scores may be suitable for treatment using immune checkpoint inhibitors.

1. Introduction

Chemokines are a large class of cytokines with chemotactic activities (1, 2), and in the past few decades, increasing evidence has accumulated to reveal the role of these chemokines in the tumor microenvironment (TME). Homologous receptors are generally expressed in cancer and stromal cells, changes in the expression of which in malignant tumors determine the recruitment and activation of leukocytes, angiogenesis, cancer cell proliferation, and metastasis (3, 4).

The TME is the primary site wherein tumor cells and the host immune system interact, into which different subsets of immune cells are recruited via the interaction between chemokines and their respective receptors. These subsets have been established to have differing effects on tumor progression,

as well as the efficacy of treatment (5, 6). For example, CXCL9 and CXCL10 promote the migration of effector T and NK cells into tumors (7, 8). The findings of several studies have revealed that elevated therapeutic responses to immune checkpoint inhibitor (ICI) treatment are associated with increased levels of the chemokines CXCL9 and CXCL10, and an increase in the number of effector T cells within the TME (9, 10). In contrast, the chemokine CXCL8 promotes an increase in tumor angiogenesis and recruits larger numbers of immunosuppressive cells to the tumor site. Accordingly, targeting CXCL8 may elevate the response to ICI treatment (11). Given these observations, it would be of particular interest to conduct a comprehensive analysis of the chemokines and tumor immune microenvironment in a pan-cancer context.

In this study, we performed a systematic pan-cancer analysis of chemokine genes in 33 tumor types selected from the Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx) databases, in which we examined gene alteration and expression, clinical features, and prognostic values. Having obtained this information, we calculated chemokine scores and assessed correlations between chemokine scores and the tumor immune microenvironment and immunotherapeutic responses, thereby providing an indication as to the effect of chemokine score on the efficacy of immunotherapy.

2. Materials And Methods

2.1 Data collection

Expression profile data and clinical information for the TCGA and GTEx cohorts were downloaded from the UCSC Xena (https://xenabrowser.net/datapages/) database. Information on the sizes of tumor and normal tissue samples in TCGA and GETx databases is provided in Supplementary Table 1. The immune cell infiltration data extracted from TCGA were obtained from the ImmuCellAI database (http://bioinfo.life.hust.edu.cn/ImmuCellAI#!/) and the TIMER2 database (http://timer.cistrome.org/); immunotherapy cohorts GSE176307 and IMvigor210 were respectively obtained from the GEO database (https://www.ncbi.nlm.nih.gov/gds/?term=GSE78220) and R package “IMvigor210CoreBiologies” (12)’; and ICB.Riaz2017 cohort data were downloaded from the TIDE database (http://tide.dfci.harvard.edu/).

2.2 Online analysis

Information pertaining to alterations in chemokine genes, including mutations, copy numbers, and methylation, was obtained from the GSCA database (http://bioinfo.life.hust.edu.cn/GSCA/#/), and correlations between the IC_{50} values of anticancer drugs and mRNA expression were determined using the GSCA cohort.

2.3 Prognostic analysis of chemokine scores

The ssGSEA function of R (version 4.1.1) package “GSVA” was used to calculate the chemokine score of each patient in the TCGA cohort. to explore The associations between chemokine scores and the survival of patients, including overall survival (OS), disease-specific survival (DSS), disease-free interval (DFI), and

progression-free interval (PFI), were determined based on univariate Cox regression (uniCox) analyses using the R packages “survminer” and “survival.”

2.4 Gene enrichment analysis

To determine the associated functions of chemokine, we performed gene set variation analysis (GSVA) using the R package “GSVA.” The HALLMARK pathways used in GSVA were obtained from the MsigDB database (http://softwchemokinee.broadinstitute.org/gsea/msigdb/index.jsp).

2.5 Tumor microenvironment analysis

To calculate the stromal and immune, tumor purity, and ESTIMATE scores of each patient in the TCGA cohort, we used the R package “ESTIMATE,” and also analyzed the association between chemokine scores and these scores. TME-related pathways were obtained, and pathway scores were calculated with reference to a previously published paper (13). We further analyzed the correlations between chemokine scores and immune cell infiltration, immunomodulatory genes, MHC genes, and chemokine/chemokine receptors at the pan-cancer level, with results being visualized using heatmaps.

2.6 Statistical analysis

Differences between different groups were compared using Student’s *t*-test using the “ggplot2” or “ggpubr” functions of R software (https://www.r-project.org/, version:4.1.1). Correlations were determined based Pearson correlation analysis. A P-value < 0.05 (two-tailed) was considered to be indicative of statistical significance.

3. Results

3.1 The differential mRNA expression and prognostic value of chemokine genes

A total of 41 chemokine genes were identified in this study, the differential expression of which we initially examined in 33 tumor types based on information obtained from the TCGA and GTEx databases. As shown in Fig. 1A, with the exception of pheochromocytoma (PCPG) and sarcoma (SARC), chemokine genes were commonly differentially expressed in most tumor types. CCL18 was highly expressed in 28 of the 33 tumors, whereas CCL16 was expressed at low levels in 23 of the 33 tumors. Using TCGA pan-cancer data, we also performed mRNA correlation analysis (Fig. 1B), and also conducted pan-cancer univariate analysis to determine the prognostic value of each gene (Fig. 2A). The results thus obtained indicated that CCL20 was a risk factor in nine of the 33 tumors, whereas CCL17 was a protective factor in seven

(Fig. 2B).

3.2 The alteration of chemokine genes

For each of the assessed chemokine genes, we obtained the following information: variant classification, variant type, SNV class, variants per sample, variant classification summary, and the top 10 mutated genes (Fig. 3A). With regards to the SNV percentage, the total deleterious mutation percentage (the number of samples with at least one deleterious mutation site/the number of samples with SNV mutation data) revealed the highest deleterious mutation frequency in CXCL1 and CXCL12 in uterine corpus endometrial carcinoma (UCEC) (Fig. 3B). Moreover, pan-cancer analysis revealed that CX3CL1 has the highest mutation frequency (10%) among the assessed chemokine genes (Fig. 3C).

We further analyzed the copy number variants (CNVs) of chemokine genes, the proportions of different types of which, including heterozygous amplification, heterozygous deletion, homozygous amplification, and homozygous deletion, in pan-cancer are shown in Fig. 4A. We accordingly found that the CNV of CXCL16 was positively correlated with the mRNA expression of this gene in 22 of the 33 tumor types (Fig. 4B). Furthermore, the CNV of homozygous or heterozygous amplification was established to be positively correlated with mRNA expression, whereas the CNV of homozygous or heterozygous deletions was negatively correlated with mRNA expression (Fig. 4C and D).

We also determined the methylation status of chemokine genes in the 33 tumor types, with the results indicating that the methylation levels were negatively correlated with their mRNA expression (Fig. 5A). The differential methylation levels of genes between the tumor and normal sample groups are shown in Fig. 5B.

3.3 The calculation, differential distribution, and survival analysis of chemokine scores

We performed ssGSEA to calculate chemokine scores for the 33 tumor types identified in the TCGA cohort. These chemokine scores were found to be highest and lowest for lung adenocarcinoma (LUAD) and acute myeloid leukemia (LAML), respectively (Fig. 6A). Moreover, we found that chemokine scores were lower for tumor tissues than in the adjacent normal tissues with respect to bladder urothelial carcinoma (BLCA), breast invasive carcinoma (BRCA), kidney chromophobe (KICH), liver hepatocellular carcinoma (LIHC), lung squamous cell carcinoma (LUSC), and UCEC (Fig. 6B-G), although were higher in esophageal carcinoma (ESCA), kidney renal clear cell carcinoma (KIRC), and stomach adenocarcinoma (STAD) (Fig. 6H-J).

The results of uniCox analysis revealed the following: (1) for OS, chemokine score was a risk factor in KIRC, UVM, THYM, GBM, LAML, and PAAD, and a protective factor in SKCM, SARC, BRCA, and OV (Fig. 7A); (2) for DSS, the chemokine score was a risk factor for KIRC, UVM, THYM, and GBM, and a protective factor in SKCM, SARC, and OV (Fig. 7B); (3) for DFI, the chemokine score was a protective factor in LIHC, COAD, and BLCA (Fig. 7C); and (4) for the PFI, the chemokine score was a risk factor for KIRC, GBM, and THYM, and a protective factor in LIHC, SKCM, ACC, BRCA, and HNSC (Fig. 7D).

3.4 Gene set variation analysis of chemokine score

To analyze the pathways potentially associated with chemokines, we performed GSVA based on 50 HALLMARK pathways. The correlations between chemokine expression and GSVA scores in pan-cancer are shown in Fig. 8. We observed that chemokine scores were positively associated with numerous immune-related pathways in pan-cancer, including IL6-JAK-STAT3 signaling, inflammatory response, IL2 STAT5 signaling, and interferon gamma response.

3.5 Relationships between chemokines and the tumor microenvironment

We also examined the association between chemokine scores and the stromal and immune scores in pan-cancer (Fig. 9A), the results of which revealed that the chemokine score was positively associated with the immune, stromal, and ESTIMATE scores in pan-cancer. We further obtained and analyzed TME-related pathways based on reference to a previously published paper (13), including immune-related, stromal-related, and DNA repair-related pathways (Fig. 9B). For example, in BLCA, immune-related signaling (immune checkpoint, CD8 T effector, and antigen processing machinery) was higher in the high-chemokine score group (Fig. 9C).

These findings indicate that chemokines are highly correlated with immune-related pathways, and we accordingly further examined the correlations between chemokine scores and immune cells in the tumor immune microenvironment. On the basis of the immune cell infiltration results obtained from TIMER2, we found chemokine scores to be positively correlated with the infiltration level of most immune cells (Fig. 10A), and reference to the ImmuCellAI database indicated that, with the exception of CD8 naive cells and neutrophils, chemokine scores were highly correlated with most immune cells at the pan-cancer level (Fig. 10B). We also analyzed the correlations between chemokine scores and immune regulation-related genes and observed a positive correlation in these gene sets, including immunosuppressive (Fig. 11A), immune-activating (Fig. 11B), and MHC (Fig. 11C) genes. These results indicated that tumor samples with high chemokine scores were rich in immune cells.

3.6. The association between chemokines and immunotherapeutic response

On the basis of our observations indicating that chemokine scores were positively correlated with most immune cell types, we hypothesized that chemokines play a significant role in determining the efficacy of immunotherapy and that patients with a high chemokine score may be sensitive to ICI treatment. To verify these suppositions, we obtained immunotherapy data and calculated the corresponding chemokine scores, which revealed that GSE176307 cohort patients with high chemokine scores had better survival status (Fig. 12A). Furthermore, Kaplan–Meier analysis of the different groups revealed that the proportion of SD/PD patients in the high-chemokine group (71%) was lower than that in the low-chemokine group (85%) (Fig. 12B), and similar results were obtained for the ICB.Riaz2017 (Fig. 12C and D) and IMvigor210CoreBiologies (Fig. 12E and F) cohorts.

4. Duscussion

The contribution of immune cells to cancer progression and treatment differs depending on subset type. Chemokines play functional roles in coordinating the recruitment of immune cells into and out of tissues as cues, as well as guiding the interaction between spatial tissues and cells (14–16). Notably, chemokines play a key role in guiding immune cell migration, which is necessary to achieve an effective antitumor immune response. However, chemokines are also involved in the generation and recruitment of immune cells that promote the development of a tumorigenic microenvironment (17, 18).

In this study, we undertook a comprehensive analysis of the correlations between chemokines and the tumor immune microenvironment using TCGA pan-cancer data. We initially assessed the differential expression and prognostic value of chemokine genes in 33 tumor types. Consistent with predictions, we detected different patterns of chemokine activity according to tumor type. For example, CCL18 was found to be highly expressed in 28 of the 33 assessed tumors, whereas CCL16 was expressed at low levels in 23 tumor types. Furthermore, CCL20 was established to be a risk factor in nine of the 33 tumors, whereas in seven tumor types, CCL17 functions as a protective factor. In addition, in the case of the TCGA cohort, we performed a comprehensive characterization of genetic changes in chemokine genes, including mutation, fusion, amplification, homozygous deletion, and multiple alterations.

We further established a chemokine score based on the ssGSEA method for pan-cancer analysis. The GSVA results obtained indicated that chemokine scores were closely associated with immune-related pathways, among which are the IL6-JAK-STAT3 signaling, inflammatory response, IL2 STAT5 signaling, and interferon gamma response pathways. Using immune cell infiltration data obtained from the ImmuCellAI and TIMER2 databases, we performed correlation analysis to examine the associations between chemokine scores and immune cell infiltration, and accordingly found that chemokine scores were closely associated with the activities of most immune cells, including TAMs, CAFs, iTregs, and endothelial cells, thereby

indicating that tumor tissues with high chemokine scores are rich in immune cells. From the perspective of immunotherapy, an immune cell-enriched TME is particularly advantageous (19–21). Thus, we predicted that those patients with high chemokine scores would be sensitive to ICI treatment, and indeed, based on our analysis of immunotherapy data, we established that those patients with high chemokine scores who underwent ICI treatment had a better survival status.

5. Conclusions

In summary, the findings of this study revealed that elevated chemokine scores are closely associated with the immune microenvironment in pan-cancer. Patients with high chemokine scores were found to be sensitive to immune checkpoint inhibitor treatment. Accordingly, the chemokine score could serve as a potential biomarker for ascertaining the efficacy of immune checkpoint inhibitor treatment in patients with tumors.

Abbreviations

TISIDB:an integrated repository portal for tumor-immune system interactions

TME:tumor microenvironment

ICI:immune checkpoint inhibitor

TCGA:the Cancer Genome Atlas

GTE:Genotype-Tissue Expression

OS:overall survival

DSS:disease-specific survival

DFI:disease-free interval

PFI:progression-free interval

CNV:copy number variant

SNV:single-nucleotide variant

LUAD:lung adenocarcinoma

LAML:acute myeloid leukemia

BLCA:bladder urothelial carcinoma

BRCA:breast invasive carcinoma

KICH:kidney chromophobe

LIHC:liver hepatocellular carcinoma

LUSC:lung squamous cell carcinoma

ESCA:esophageal carcinoma

KIRC:kidney renal clear cell carcinoma

STAD:stomach adenocarcinoma

Declarations

Data sharing statement

All the data will be provided on reasonable request from the corresponding author.

Ethical Approval and Consent to participate

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Consent for publication

Not applicable.

Availability of supporting data

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article

Competing interests

The authors declare that they have no conflicts of interest.

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Authors' contributions

TWG designed the study. TWG and WLL contributed to data analysis and interpretation. WLL and ZJJ assisted in collection and assembly of data. TWG and WLL wrote and edited the manuscript. LDL obtained funding support. All authors participated in preparing the manuscript and approved the final manuscript

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Figures

Figure 1

The expression and correlation of chemokine genes.

A. Differential expression of chemokine genes in 33 tumor types based on TCGA and GTEx cohorts. B. Correlation between the mRNA expression of chemokine genes in pan-cancer. The darker the color, the stronger is the correlation.

Figure 2

Chemokine gene-based prognosis.

Heatmap showing the uniCox results obtained for chemokine genes in each tumor type. B. The pan-cancer risk score (the number of tumors in which genes are risk factors minus the number of tumors in which genes are protective factors) for each chemokine gene.

Figure 3

The mutation of chemokine genes in pan-cancer.

A. Information relating to Variant Classification, Variant Type, SNV class, Variant per sample, Variant Classification summary, and Top 10 mutated genes in pan-cancer. B. The frequency of deleterious mutations in the indicated tumor types. C. Oncoplot showing the mutation distribution of the top 10 mutated genes in pan-cancer.

Figure 4

The copy number variants of chemokine genes in pan-cancer.

A. A pie chart summarizing the copy number variants (CNVs) of chemokine genes in the indicated tumor types. B. The correlation between CNV and gene expression. C. A profile of the heterozygous CNVs of TRP family genes in the indicated tumor types.

D. A profile of the homozygous CNVs of TRP family genes in the indicated tumor types.

Figure 5

The methylation levels of chemokine genes in pan-cancer.

A. Correlation between the methylation and mRNA expression of each gene. B. A summary of the differences in gene methylation levels between tumor and normal samples of the indicated tumor types.

Figure 6

The differential distribution of chemokine scores.

A. The chemokine score distribution in 33 tumor types in the TCGA cohort. B-J. The differential distribution of chemokine scores in paired tumor and adjacent normal tissues. *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001.

Figure 7

The uniCox analysis of chemokine scores.

A-D. Forest plots showing the results of uniCox analysis of chemokine scores in pan-cancer. (A) overall survival (OS), (B) disease-specific survival (DSS), (C) disease-free interval (DFI), and (D) progression-free interval (PFI).

Figure 8

Gene set variation analysis of chemokine scores.

A. A heatmap depicting the correlation between chemokine scores and 50 HALLMARK pathways in pan-cancer. *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001.

Figure 9

Tumor immune microenvironment analysis of chemokine scores.

A. A heatmap depicting the correlation between chemokine, immune, stromal, ESTIMATE, and tumor purity scores in pan-cancer. B. A heatmap depicting the correlation between chemokine score and tumor immune microenvironment (TME)-related pathways. C. Differences in the TME-related pathway scores in high and low chemokine groups. *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001.

Figure 10

Immune infiltration analysis.

A. Correlation between chemokine scores and immune cell infiltration data obtained from the TIMER2 database. B. Correlation between chemokine scores and immune cell infiltration data obtained from the ImmuCellAI database. *P < 0.05, **P < 0.01,

***P < 0.001, ****P < 0.0001.

Figure 11

Correlation between chemokine genes and immune cell infiltration.

A-C. Correlation between chemokine scores and immune-related genes in pan-cancer: immunosuppressive genes (A), immune-activating genes (B), and MHC genes. (C).

*P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001.

Figure 12

The association between chemokine scores and immune checkpoint inhibitor treatment response.

A. Kaplan–Meier analysis of chemokine scores in the GSE176307 cohort. B. The percentages of CR/PR and SD/PD patients in high- and low-chemokine score groups in the GSE176307 cohort. C. Kaplan–Meier analysis of chemokine scores in the ICB.Riaz2017 cohort. D. The percentages of responses (Yes or No) in the high- and low-chemokine score groups of patients in the ICB.Riaz2017 cohort. E. Kaplan–Meier analysis of the chemokine scores in the IMvigor210CoreBiologies cohort. F. The percentages of CR/PR and SD/PD patients in high- and low-chemokine score groups in the IMvigor210CoreBiologies cohort.

Supplementary Files

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- SupplementaryTable1.xlsx