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Role of CD68 in tumor immunity and prognosis prediction: A Pan-cancer analysis

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Abstract

CD68 plays a critical role in promoting phagocytosis. However, the function of CD68 in tumor immunity and prognosis remains unknown. This study systematically analyzed CD68 expression among 33 tumor and normal tissues from the Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx) datasets. In addition, the relationship between the expression of CD68 and cancer prognosis, immune infiltration, checkpoint markers, drug response were explored. Upregulated levels of CD68 were observed in various cancer types, which were verified through tumor tissue chips using Immunohistochemistry. High expression of CD68 in tumor samples correlates with an adverse prognosis in GBM, KIRC, LGG, LIHC, LUSC, THCA, and THYM while with a better prognosis in KICH. The top three negatively enriched KEGG terms in the high CD68 subgroup were chemokine signaling pathway, cytokine-cytokine receptor interaction, cell adhesion molecules cams, and the top negatively enriched HALLMARK terms included complement, allograft rejection, and inflammatory response. Based on CD68 levels, a series of targeted drugs and small molecule drugs with promising therapeutic effects were predicted. The clinical prognosis and immune infiltration of high expression levels of CD68 differ across different tumor types. Inhibiting the CD68-dependent signaling could be a promising therapeutic strategy of immunotherapy in many tumor types.

Key word: CD68, prognosis, pan-cancer, tumor microenvironment, immunotherapy

Introduction

According to the latest study in 2019, cancer has become the first or second leading cause of death in more than 112 countries for less than 70 years old ¹. Worldwide, more than 19 million new cancer cases and 10 million cancer deaths occurred in 2020 ². Even undergoing a series of traditional treatment methods, including radiotherapy, chemotherapy, biological therapy, and surgery, the effect of tumor therapy is still unsatisfactory ^{3,4}. Tumor immunotherapeutic strategies such as the focus on programmed cell death protein 1 (PD1) have proven to be a novel and promising treatment for tumors ^{5,6}. With the rapid development of high-throughput sequencing technology, more and more immune-associated molecules related to tumor prognosis have been discovered, which may play an irreplaceable role in tumor immunotherapy. The cluster of differentiation 68(CD68), also known as GP110, LAMP4, or SCARD1, is a 110 kD transmembrane glycoprotein widely expressed in the monocyte cell types

such as macrophages, microglia, and osteoclasts ⁷. CD68 plays an essential role in various physiological and pathological processes, including atherosclerosis formation ⁸, inflammation and auto-immunity ⁹, bone-resorbing promotion ¹⁰, tumor progression ^{11,12}. Bone marrow-derived macrophages (BMMs) are the most common type among tumor-infiltrating immune cells in the tumor microenvironment (TME) and are vital factors that mediate the antitumor immune response ¹³⁻¹⁵. Recent studies found that CD68 is overexpressed in tumor-associated macrophages (TAMs) and tumor cells. High levels of CD68 are associated with higher tumor grade, larger tumor size, Ki67 positivity, and other malignant features, which indicate tumor progression and aggressiveness ¹⁶⁻¹⁹. TAMs, identified by CD68 expression, can be divided into two subtypes: classically activated type 1 (M1-like) macrophages and alternatively activated type 2 (M2-like) macrophages. M1-like macrophages, with proinflammatory characteristics that express high levels of free radicals and major histocompatibility complex molecules, contribute to antitumor activity ^{20,21}. In contrast, M2-like macrophages, which release multiply anti-inflammatory cytokines and chemokines, were reported to promote tumor growth and metastasis ^{22,23}. Increasing evidence has shown that CD68 is a promising tumor-associated diagnostic and prognostic marker in cancer. However, the signaling pathways that CD68 involved in the tumor immunity and progress remain still far from understood.

In this study, we studied the expression of CD68 in 33 cancer types using large-scale RNA-sequencing (RNA-seq) data from the public dataset-TCGA. Upregulated levels of CD68 were observed in various cancer types, which were observed in the TCGA database and our tumor tissue chips. Meanwhile, we discussed the value of CD68 in prognostic prediction in pan-cancer. Moreover, the relationship between the expression levels of CD68 and the infiltration of immune cells in the pan-cancer microenvironment was observed. Finally, we analyzed the correlation of a series of predicted drugs and CD68 expression, which might be used for tumor immunotherapy in the future.

Materials and Methods

Collection of sample and patient data

The clinicopathological features and RNA sequencing (RNA-seq) data of the 33 types of cancers were chosen from the TCGA dataset(<http://cancergenome.nih.gov>). As the data from normal tissue is relatively insufficient, the RNA-seq data of normal human tissues were additionally added from the GTEx dataset (<https://www.gtexportal.org/>) to analyze the expression levels CD68 between tumor and normal tissues. A tumor tissue chip (Catalog NO. BCN963) contains multiple organ tumor arrays with matched normal tissues that were used to verify the expression of CD68. Informed consent of all subjects has been obtained in this study.

Recognition of relevant features

The gene expression data of CD68 were extracted from TCGA and GTEx databases to form an expression matrix using ONCOMING (<https://www.oncomine.org/>), GEPIA (<http://gepia.cancer-pku.cn/>) and R package (4.0.4). The genetic mutation aspects of CD68 were observed from the public database-CBIOPORTAL (<https://www.cbioportal.org/>). The Kaplan-Meier (KM) analysis by the log-rank test

was used to compare the disease-free interval (DFI), progression-free interval (PFI), disease-specific survival (DSS), and overall survival (OS) among patients. Univariate Cox model was used to calculate the relationship between CD68 expression levels and patient survival. The immune infiltrates among 33 types of cancers were studied by Tumor Immune Estimation Resource (TIMER 2.0, <https://cistrome.shinyapps.io/timer/>)²⁴ and CIBERSORT²⁵. The ESTIMATE algorithm was applied to estimate the stromal and immune cells in the tumor microenvironment and calculated the stromal scores, immune scores, and estimate scores. Gene set enrichment analysis (GSEA) was selected to display the involved biological functions and pathways of CD68. This analysis was implemented in Sangerbox (<http://sangerbox.com/>) based on the molecular signatures database (MSigDB) H (hallmark gene sets) and Kyoto Encyclopedia of Genes and Genomes database (KEGG). The relationship between CD68 expression and drug responses was predicted from CELLMINER(<http://discover.nci.nih.gov/cellminer/>) by R language.

Statistical analysis

A Student's t-test was performed to explore the correlation between CD68 expression and drugs. Kruskal-Wallis test was adopted to compare the expression levels of CD68 in tumor and normal tissues. Meanwhile, KM curves, the Log-rank test, and the Cox proportional hazards regression model were applied to analyze the survival conditions. In addition, the Spearman test was used for correlation analysis. All analyses were performed under the R language. All statistical tests were two-sided, and $p < 0.05$ was considered a significant difference.

Results

Expression of CD68 in pan-cancer

First, we observed the expression of CD68 in pan-cancer using the Oncomine dataset and found that the levels of CD68 were relatively higher in the brain and central nervous system (CNS) cancer, breast cancer (BRCA), kidney cancer, lymphoma, pancreatic cancer than in normal tissues. Meanwhile, other studies also indicated that the expression of CD68 was downregulated in colorectal cancer, kidney cancer, leukemia, and lung cancer (Figure 1A). In addition, we matched the GTEx normal samples with the TCGA tumor samples (Figure 1B). We found that the levels of CD68 in colon adenocarcinoma (COAD), glioblastoma multiforme (GBM), kidney renal clear cell carcinoma (KIRC), kidney renal papillary cell carcinoma (KIRP), brain lower-grade glioma (LGG), ovarian serous cystadenocarcinoma (OV), pancreatic adenocarcinoma (PAAD), rectum adenocarcinoma (READ), skin cutaneous melanoma (SKCM), stomach adenocarcinoma (STAD), testicular germ cell tumors (TGCT) and uterine carcinosarcoma (UCS) were significantly elevated ($p < 0.01$) in tumor tissues than in normal tissues. On the contrary, CD68 was significantly declined ($p < 0.001$) in thymoma (THYM) compared to GTEx normal controls. Moreover, the immunohistochemical results indicated that the expression of CD68 was obviously enhanced in COAD, GBM, KIRC, LGG, OV, PAAD, READ, SKCM, and STAD

compared to their normal controls (Figure 1C).

Mutation profile and prognostic value of CD68 in pan-cancer

Then, we checked the landscape of CD68 aspects in different cancer types from the TCGA database using cBioportal (Figure 2). The data showed that PRAD and diffuse large B-Cell lymphoma had a high mutation level with CD68 deep deletion of more than 4% (Figure 2A and 2B). A total of 45 mutation sites (including 31 missense, 11 truncating, two splices, and 1 inflame) were found between amino acids 0 and 354 (Figure 2C). Next, to further understand the prognostic value of CD68 in pan-cancer, we downloaded RNA-seq and clinical data of CD68 from the TCGA dataset. As shown in Figure 3A-I, the elevated levels of CD68 were significantly related to poorer OS in GBM (HR=1.05, 95%CI=1.00-1.09, P=0.0370), KIRC(HR=1.04, 95%CI=1.02-1.06, P=0.0007), LGG(HR=1.18, 95%CI=1.06-1.31, P=0.0020), LIHC(HR=1.06, 95%CI=1.02-1.11, P=0.0058), LUSC(HR=1.04, 95%CI=1.00-1.08, P=0.0470), THCA(HR=1.17, 95%CI=1.06-1.29, P=0.0023) and THYM(HR=1.47, 95%CI=1.08-2.00, P=0.0130). On the contrary, upregulated CD68 expression was associated with a favorable prognosis in KICH (HR=1.40, 95%CI=1.05-1.87, P=0.0220). In addition, as shown in Figure 3J and Supplement Figure 1C-I, the high expression of CD68 was related with a unfavorable DSS in KIRC(HR=1.04, 95%CI=1.02-1.07, P=0.0052), GBM(HR=1.05, 95%CI=1.00-1.10, P=0.0490), LGG(HR=1.19, 95%CI=1.06-1.34, P=0.0410) and THYM(HR=1.69, 95%CI=1.04-2.77, P=0.0360), while related with a favorable DSS in CESC(HR=0.83, 95%CI=0.70-0.99, P=0.0380) and KICH(HR=1.46, 95%CI=1.09-1.96, P=0.0110). Furthermore, we observed the prognostic value of CD68 in DFI (Supplement Figure 1A) and PFI (Supplement Figure 1B). The results showed that high levels of CD68 were associated with a poorer DFI in GBM, LGG, THYM and a better DFI in KICH (Supplement Figure 1E-1I). Meanwhile, the high levels of CD68 were associated with a poorer PFI in CHOL, LIHC, STAD, and a better DFI in CESC (Supplement Figure 1J-1M).

Relationship between CD68 expression and immune cell infiltration

Next, we explored the landscape of CD68 in the tumor microenvironment in all tumor types based on the TIMER2.0 database. As shown in Figure 4, the CD68 expression was positively related to multiplying immune cells infiltration, including dendritic cells, monocyte, macrophage, and neutrophil. However, the CD68 expression was negatively associated with the infiltration of myeloid-derived suppressor cells (MDSC). Next, we analyzed the correlation of CD68 levels and immune cell infiltration in the tumor microenvironment in 33 cancer types. The results indicated that the expression of CD68 was positively related to the abundance B cell, CD4+ T cell, CD8+ T cell, dendritic cell, macrophage, and neutrophil in many tumor types. As shown in Figure 5A, the three most significantly related tumors are adrenocortical carcinoma (ACC), BRCA, and CESC. The details in other tumor types are shown in Supplement Figure 2. We further calculated the stromal score, immune score, and estimate score of 33 cancer types by ESTIMATE algorithm. As shown in Figure 5B, the top three tumor types that CD68 expression positively correlated with stromal score are BLCA, BRCA, and GBM ($p < 0.001$); the top three tumor types that CD68

expression positively correlated with immune score are ACC, BLCA, and BRCA($p < 0.001$); the top three tumor types that CD68 expression positively correlated with estimate score are BLCA, BRCA, and CESC($p < 0.001$). Data in Supplement Figure 3 showed that the expression of CD68 was significantly and positively correlated with the stromal score in all tumor types except CHOL and mesothelioma (MESO). In addition, the expression of CD68 was significantly and positively correlated with immune scores in all tumor types (Supplement Figure 4). Moreover, the expression of CD68 was significantly and positively correlated with immune scores in all tumor types (Supplement Figure 5). These indicated that CD68 has a close relationship with immune infiltrates in the tumor microenvironment and might act as a promising immunotherapy target.

Neoantigen is a neoantigen encoded by a mutated gene of tumor cells, which plays a crucial role in tumor immunotherapy. We then explored the relationship between CD68 expression and the number of neoantigen in human cancers (Figure 6). Our results indicated that high levels of CD68 were significantly and positively related to the number of neoantigen in LUAD, KIRP, CESC, and PRAD ($p < 0.05$).

The relationship between CD68 expression and checkpoint gene markers, tumor mutation burden, and microsatellite instability

To further elaborated the potential immune mechanisms of CD68, we next compared the association of CD68 expression with various checkpoint markers in different cancer types (Figure 7A). The results showed that CD68 expression positively correlates with the expression of LARI1, HAVCR2, LGALS9, PD1 in most of the 33 tumor types. We also studied the relationship between CD68 expression and five DNA mismatch repair (MMR) markers (Figure 7B). CD68 levels were significantly and negatively correlated with mutL homolog 1 (MLH1), mutS homolog 2 (MSH2), mutS homolog 6 (MSH6), postmeiotic segregation increased 2 (PMS2), and epithelial cell adhesion molecule (EPCAM) in BRCA, CESC, KIRC, OV and THCA($p < 0.05$).

However, the CD68 levels were significantly and positively correlated with MSH6 in KICH and READ($p < 0.05$). In addition, we studied the correlation between tumor mutation burden (TMB) and microsatellite instability (MSI) with CD68 levels.

Moreover, the CD68 expression was positively related($p < 0.05$) with TMB in UCEC, SKCM, SARC, READ, PRAD, LGG, KIRP, KIRC, COAD, CESC, BRCA while negatively related($p < 0.05$) with TMB in THCA, READ, LIHC, LAML, GBM

(Figure 7C). CD68 expression was positively related($p < 0.05$) with MSI in UCEC,

READ, LIHC, COAD while negatively related($p < 0.05$) with MSI in KIRC, LUAD,

LUSC, TGCT (Figure 7D).

Functional analysis by gene set enrichment analysis and drug response of CD68

Finally, we analyzed the related functional signaling pathways of CD68 through GSEA based on KEGG and HALLMARK databases in pan-cancer. The top three negatively enriched KEGG terms($p < 0.001$) in upregulated CD68 subgroup are chemokine signaling pathway, cytokine-cytokine receptor interaction, and cell adhesion molecules (Figure 8A), and the top three positively enriched KEGG terms($p < 0.001$) in upregulated CD68 subgroup are aminoacyl tRNA biosynthesis, valine leucine, and isoleucine biosynthesis and taste transduction (Figure 8B). In addition, the top three negatively enriched HALLMARK terms($p < 0.001$) in upregulated CD68 subgroup are a complement, allograft rejection, and inflammatory response (Figure 8C), and the top three positively enriched HALLMARK terms($p < 0.001$) in upregulated CD68 subgroup are pancreas beta cells, MYC targets V1 and V2 (Figure 8D). The top 5 enriched pathways are shown in Supplement Table 1. The results from drug response analysis by CellMiner suggested that a lot of drugs were associated with CD68 expression, of which the top 16 were exhibited in Supplement Figure 6. In addition, the top 20 related drugs are shown in Supplement Table 2.

Discussion

In this study, we explored the role of CD68 in clinical outcome prediction and immune cell infiltration in pan-cancer from TCGA and GETx databases. The results indicated that elevated CD68 was observed in many tumor types, including COAD, GBM, KIRC, KIRP, LGG, OV, PAAD, READ, SKCM, STAD, TGCT, UCS, and was associated with a more unsatisfactory clinical outcome in GBM, KIRC, LGG, LIHC, LUSC, THCA, and THYM. Meanwhile, we calculated the infiltration of the immune cells in the tumor microenvironment. We found that high levels of CD68 were associated with a lot of immune cells in the tumor microenvironment, such as monocyte, abundance B cell, CD4⁺ T cell, CD8⁺ T cell, dendritic cell, macrophage, and neutrophil. Moreover, the upregulated expression of CD68 was closely related to the stromal score, immune score, and estimate score in many types of human cancer. These results were consistent with previous studies in CD68²⁶⁻²⁸, which indicated that CD68 might be a future novel and promising immunotherapy target.

Neoantigens, kinds of non-autologous proteins with specific characteristics, are generated from the tumor cell genome through non-synonymous mutations²⁹ and play an essential role in tumor immunotherapy²⁹⁻³¹. The present work illustrated that high expression levels of CD68 were significantly and positively related to the number of neoantigen in LUAD, KIRP, CESC, and PRAD. In addition, the mutation landscape of CD68 in pan tumor types was also displayed in this study. Anti-immune checkpoint therapy has become a necessary treatment in fighting cancer in recent years^{29,32,33}. To the full clarified the immune value of CD68 in pan-cancer, we next studied the correlation between CD68 expression and large numbers of immune checkpoints in

pan-cancer and found that high levels of CD68 were significantly and positively related with some key checkpoints, including LARI1, HAVCR2, LGALS9, PD1 in the most of 33 tumor types.

Furthermore, the CD68 expression was majority negatively related to DNA mismatch repair (MMR) markers in most types of cancer. Increasing studies found that TMB and MSI are emerging clinical biomarkers in immunotherapy, clinical outcome, and chemotherapy sensitivity in various tumor types³⁴⁻³⁶. This present study also found that CD68 expression was correlated with TMB and MSI in many cancer types, which might provide probable and potential evidence for predicting the efficacy of tumor immunotherapy.

The specific mechanisms of CD68 in tumor growth and metastasis are still far from understand until right now. Our study also explored a majority of pathways related to the expression of CD68 in pan-cancer, which might help figure out the exact function of CD68 and downstream signaling pathways in the future. In addition, there are no small molecule drugs that were specifically targeting CD68 in tumor therapy. Finally, we identified a series of targeted medicines and small-molecule drugs with promising efficacy predicted by CD68 levels, which the FDA proved. These drugs might serve a key role in tumor chemotherapy and are conducive to improving the treatment of tumors.

There are several limitations to this study. Firstly, the mRNA expression levels of CD68 were assessed from public databases and only verified by tumor tissue chips, not validated in vivo and in vitro studies. Secondly, the role of CD68 in tumor immune cell infiltration in pan-cancer was not verified by cell and animal experiments in this study. More studies focus on the specific signaling pathways of CD68 in pan-cancer need to be explored clearly in the future.

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Author contributions:

J.Z. and F.L. designed and performed the research and wrote the manuscript. Data curation and validation were performed by S.L. All authors contributed to writing and critically revising the manuscript.

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Availability of data and materials:

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest:

None.

Ethical approval and ethical standards:

The study with primary human tissues was approved by the ethics committee of the

Xiangya Hospital, Central South University, and the procedures with human samples were performed in accordance with the ethical standards of the ethics committee and the Helsinki Declaration of 1975 and its later amendments.

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Figure legends:

Figure 1. CD68 expression in tumor and normal tissues based on the TCGA and GETx databases.

(A) Expression of CD68 from the Oncomine dataset. (B) Expression of CD68 from the TCGA and GTEx database. (C) Expression of CD68 from tumor tissue chip using immunohistochemistry. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Figure 2. Mutation landscape of CD68 in pan-cancer.

(A) Mutation frequency of CD68 in pan-cancer from TCGA database based on the cBioPortal database. (B) The whole mutation count of CD68 from the TCGA database is based on the cBioPortal analysis. (C) Mutation aspect of CD68 in pan-cancer across protein domains.

Figure 3. Survival analysis of CD68 in pan-cancer from TCGA database.

(A) Forest plot compared the low and high expression of CD68 on overall survival across pan-cancer. (B-I) Kaplan-Meier Method displayed the prognostic value of overall survival in GBM(B), KICH(C), KIRC(D), LGG(E), LIHC(F), LUSC(G), THCA(H), THYM(I). (J) Forest plot compared the low and high expression of CD68 on disease-specific survival across pan-cancer. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Figure 4. The relationship between CD68 and immune infiltration based on TIMER2.0 in pan-cancer.

(A) The correlation between CD68 with B cell, CD4⁺ T cell, CD8⁺ T cell, dendritic cell, monocyte, macrophage in pan-cancer. (B) The correlation between CD68 with NK cell, neutrophil, Tregs, mast cell, NKT, Tfh, $\gamma\delta$ T, HSC, Endo, progenitor, Eos, CAF, and MDSC in pan-cancer.

Figure 5. Correlation of CD68 expression with immune infiltration level based on CIBERSORT in pan-cancer.

(A) CD68 expression is significantly positively correlated with B cell, CD4⁺ T cell, CD8⁺ T cell, dendritic cell, monocyte, macrophage in ACC, BRCA, and CESC. (B) The correlation between CD68 with the stromal score, immune score, and estimate score in pan-cancer.

Figure 6. Relationship between neoantigen count and CD68 expression in pan-cancer.

(A) Relationship between neoantigen count and CD68 expression in GBM, BRCA, COAD, LIHC, and BLCA. (B) Relationship between neoantigen count and CD68 expression in OV, KIRC, READ, SKCM, and PRAD. (C) Relationship

between neoantigen count and CD68 expression in LUAD, KIRP, STAD, CESC, and LGG. (D) Relationship between neoantigen count and CD68 expression in LUSC, UCEC, HNSC, and THCA.

Figure 7. Relationship between immune checkpoint, DNA mismatch repair markers, tumor mutation burden, microsatellite instability, and CD68 expression in pan-cancer.

(A) Correlation of CD68 expression with various immune checkpoints in pan-cancer. (B) Correlation of CD68 expression with DNA mismatch repair markers in pan-cancer. (C) Correlation of CD68 expression with tumor mutation burden in pan-cancer. (D) Correlation of CD68 expression with microsatellite instability in pan-cancer. * $p < 0.05$, ** $p < 0.01$, * $p < 0.001$.**

Figure 8. Functional enrichment of KEGG and HALLMARK terms on CD68 based on GSEA in pan-cancer.

(A) The top three negative enriched KEGG terms on CD68 in pan-cancer. (B) The top four positive enriched KEGG terms on CD68 in pan-cancer. (C) The top three negative enriched HALLMARK terms on CD68 in pan-cancer. (D) The top four positive enriched HALLMARK terms on CD68 in pan-cancer.

Figures

Figure 1

CD68 expression in tumor and normal tissues based on the TCGA and GETx databases. (A) Expression of CD68 from the Oncomine dataset. (B) Expression of CD68 from the TCGA and GTEx database. (C) Expression of CD68 from tumor tissue chip using immunohistochemistry. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Figure 2

Mutation landscape of CD68 in pan-cancer. (A) Mutation frequency of CD68 in pan-cancer from TCGA database based on the cBioPortal database. (B) The whole mutation count of CD68 from the TCGA database is based on the cBioPortal analysis. (C) Mutation aspect of CD68 in pan-cancer across protein domains.

Figure 3

Survival analysis of CD68 in pan-cancer from TCGA database. (A) Forest plot compared the low and high expression of CD68 on overall survival across pan-cancer. (B-I) Kaplan-Meier Method displayed the prognostic value of overall survival in GBM(B), KICH(C), KIRC(D), LGG(E), LIHC(F), LUSC(G), THCA(H), THYM(I). (J) Forest plot compared the low and high expression of CD68 on disease-specific survival across pan-cancer. *p < 0.05, **p < 0.01, ***p < 0.001.

Figure 4

The relationship between CD68 and immune infiltration based on TIMER2.0 in pan-cancer. (A) The correlation between CD68 with B cell, CD4+ T cell, CD8+ T cell, dendritic cell, monocyte, macrophage in pan-cancer. (B) The correlation between CD68 with NK cell, neutrophil, Tregs, mast cell, NKT, Tfh, $\gamma\delta$ T, HSC, Endo, progenitor, Eos, CAF, and MDSC in pan-cancer.

Figure 5

Correlation of CD68 expression with immune infiltration level based on CIBERSORT in pan-cancer. (A) CD68 expression is significantly positively correlated with B cell, CD4+ T cell, CD8+ T cell, dendritic cell, monocyte, macrophage in ACC, BRCA, and CESC. (B) The correlation between CD68 with the stromal score, immune score, and estimate score in pan-cancer.

Figure 6

Relationship between neoantigen count and CD68 expression in pan-cancer. (A) Relationship between neoantigen count and CD68 expression in GBM, BRCA, COAD, LIHC, and BLCA. (B) Relationship between neoantigen count and CD68 expression in OV, KIRC, READ, SKCM, and PRAD. (C) Relationship between neoantigen count and CD68 expression in LUAD, KIRP, STAD, CESC, and LGG. (D) Relationship between neoantigen count and CD68 expression in LUSC, UCEC, HNSC, and THCA.

Figure 7

Relationship between immune checkpoint, DNA mismatch repair markers, tumor mutation burden, microsatellite instability, and CD68 expression in pan-cancer. (A) Correlation of CD68 expression with various immune checkpoints in pan-cancer. (B) Correlation of CD68 expression with DNA mismatch repair markers in pan-cancer. (C) Correlation of CD68 expression with tumor mutation burden in pan-cancer. (D) Correlation of CD68 expression with microsatellite instability in pan-cancer. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Figure 8

Functional enrichment of KEGG and HALLMARK terms on CD68 based on GSEA in pan-cancer. (A) The top three negative enriched KEGG terms on CD68 in pan-cancer. (B) The top four positive enriched KEGG terms on CD68 in pan-cancer. (C) The top three negative enriched HALLMARK terms on CD68 in pan-cancer. (D) The top four positive enriched HALLMARK terms on CD68 in pan-cancer.

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