CORO2A is a pan-cancer prognostic biomarker and correlates with immune infiltration

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Abstract

Background. Coronin 2A (CORO2A) is a member of the coronin family and reportedly functions as an oncogene in certain malignancies, although its correlation with prognosis and immune infiltration in different cancers remains unclear.

Methods. Data were collected from the University of California Santa Cruz (UCSC), Human Protein Atlas (HPA), Tumor Immune Estimation Resource (TIMER), Tumor-Immune System Interactions (TISIDB) and Gene Set Enrichment Analysis (GSEA) databases. The differential expression of CORO2A, survival, clinical parameters, tumor mutational burden (TMB), microsatellite instability (MSI), mismatch repair (MMR) genes, DNA methyltransferases (DNMTs), tumor microenvironment (TME), immune-related genes (IRGs), immune infiltration, pathways and functions were analyzed using the R language software.

Results. CORO2A was overexpressed in various malignancies, and correlated with clinical parameters, overall survival, disease-specific survival and progression-free survival in certain cancers. Furthermore, CORO2A was significantly correlated to the TMB, MSI, MMR genes, DNMTs, immune and stromal scores, IRGs and immune infiltration. GSEA further showed that CORO2A was associated with various immune-related pathways and functions in different cancer types.

Conclusion. CORO2A is a promising prognostic and immunological marker for human cancers.

1. Introduction

Cancer is the major cause of deaths worldwide, and an estimated 19.3 million new cases were diagnosed in 2020 alone [1]. Cancers of the lung, pancreas and liver are the most common, and are associated with high mortality rates [2]. Conventional therapies, including surgery, chemotherapy and radiotherapy, remain the first-line of treatment for most cancer patients. Despite continuing improvements in diagnosis and treatment methods, cancer recurrence and drug resistance significantly worsen patient prognosis [3]. Therefore, it is crucial to identify novel diagnostic markers and therapeutic targets for tumor cells. For instance, immunotherapeutic strategies such as immune checkpoint blockers, CAR T-cells, tumor vaccines, etc. are increasingly being considered for cancer treatment [4, 5]. In addition, several targeted therapies have also shown encouraging results in clinical trials [6].

Coronin 2A (CORO2A) is a member of the coronin family and part of the N-CoR (nuclear receptor co repressor) complex [7]. In humans, the coronin family consists of seven proteins containing WD-repeat domains that regulate actin-based cellular processes [8]. CORO2A not only mediates actin-dependent activation of inflammatory response genes [9] but is also involved in epithelial-mesenchymal transition (EMT). One study showed that CORO2A regulates the migration of breast cancer cells through multiple pathways involving several miRNAs and MYC transcription factors [7]. Furthermore, siRNA-mediated knockdown of CORO2A suppressed the migration and invasion of oral squamous cell carcinoma (OSCC) cells, and CORO2A expression was controlled in these cells by the tumor-suppressive miR-125b-5p and miR-140-5p through 3'-UTR binding [8]. Despite evidence pointing to a role of CORO2A in tumor proliferation, invasion and migration, the pan-cancer expression levels and potential functions of CORO2A remain unclear.

The tumor mutational burden (TMB) and microsatellite instability (MSI) of tumor cells, and aberrations in mismatch repair (MMR) genes and DNA methyltransferases (DNMTs) influence tumor initiation and progression [10–13], and can predict patient response to immune checkpoint blockade (ICB). Given the prognostic roles of the tumor microenvironment (TME) and anti-tumor immune responses, immune checkpoint inhibitors (ICIs) are increasingly being incorporated as the first line treatment for various cancers [14, 15]. For instance, the inhibitors of CTLA4, PD-L1, and PD-1 have exhibited superior efficacy against multiple solid tumors, including melanoma, renal cell carcinoma, and non-small-cell lung cancer [16, 17]. Unfortunately, only a small fraction of cancer patients are responsive to immunotherapy [18, 19], which warrants the identification of more effective targets. Furthermore, the tumor-infiltrating immune cells play a crucial role in the anti-tumor immune responses, as well as in cancer progression [20–22].

In this study, we systematically analyzed the pan-cancer expression level of CORO2A and its association with the clinical parameters, prognostic indicators and immune landscape, and predicted its functions and pathways in cancer using publicly available datasets and bioinformatics tools. Our findings indicated that CORO2A expression correlated with clinical prognosis and immune infiltration in multiple cancers, indicating that it is a potential pan-cancer prognostic biomarker.

2. Materials And Methods

2.1. Data processing

The RNA-sequencing data, clinicopathological and survival information, and the somatic mutations related to 33 cancers were downloaded from UCSC (https://xena.ucsc.edu/, originated from TCGA database). The CORO2A gene expression data were extracted using Strawberry Perl (Version 5.32.1.1, http://strawberryperl.com/), and plotted into a data matrix for subsequent analyses. Wilcoxon test was used to estimate the differential CORO2A expression between tumor specimens and matched normal controls, and the correlation between CORO2A expression and clinical parameters in distinct cancer types. \( P \) value < 0.05 was the cut off. The correlation between the immune-related genes (IRGs) and CORO2A was also analyzed in TISIDB (http://cis.hku.hk/TISIDB/). Finally, the TIMER database (https://cistrome.shinyapps.io/timer/) was used to analyze the correlation between CORO2A gene expression and the immune cell infiltration in multiple cancers.

2.2. Survival analysis

The overall survival (OS), disease-specific survival (DSS) and progression-free survival (PFS) data for each sample were downloaded from UCSC. The correlation between CORO2A expression and patient prognosis was analyzed by Cox regression. According to the median expression level, the patients were divided into CORO2A\textsuperscript{high} and CORO2A\textsuperscript{low} groups. The survival rates of the two groups were compared by the Kaplan-Meier (KM) method.
2.3. Immunohistochemistry (IHC)

Images of slides from breast invasive carcinoma (BRCA), glioblastoma multiforme (GBM), kidney chromophobe cell carcinoma (KICH), kidney renal papillary cell carcinoma (KIRC), pancreatic adenocarcinoma (PAAD), testicular germ cell tumors (TGCT), and the corresponding normal tissues immuno-stained for CORO2A were downloaded from the Human Protein Atlas database (HPA, http://www.proteinatlas.org/) and analyzed.

2.4. Correlation between CORO2A expression and genetic parameters

TMB scores were calculated using a Perl script and corrected by dividing by the total length of exons. MSI scores were determined for all samples based on somatic mutation data downloaded from UCSC, and the correlation between CORO2A expression, TMB and MSI were analyzed using Spearman's rank correlation coefficient. Expression profile data from UCSC were used to evaluate the levels of the MMR genes and DNMTs in different cancers, and the correlation between CORO2A, MMR genes and DNMTs were determined as above.

2.5. Correlation between CORO2A expression and immunity

Estimation of Stromal and Immune Cells in Malignant Tumor Tissues Using Expression Data (ESTIMATE) algorithm was used to calculate immune and stromal scores for each tumor sample. The correlation between CORO2A expression and the two scores were evaluated according to the degree of immune infiltration. IRGs, including the immunosuppressive genes, immune activation genes and MHC genes, and their correlation with CORO2A expression were explored on the TISIDB. Finally, the relative scores for 22 immune cell types in 33 cancers were calculated using CIBERSORT. The correlation between CORO2A expression and the infiltration levels of each immune cell population was also determined.

2.6. Gene set enrichment analysis (GSEA)

GSEA was performed to explore the pan-cancer biological functions of CORO2A. Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) gene sets were downloaded from the GSEA website (https://www.gsea-msigdb.org/gsea/downloads.jsp). Gene sets with a normal P-value < 0.05 and false discovery rate (FDR) < 0.05 were considered significantly enriched. The top five significantly enriched pathways identified by GO and KEGG in each cancer were considered.

2.7. Statistical analysis

All expression data were normalized by log2 (TPM + 1) transformation. Normal tissues and cancer tissues were compared using two sets of Wilcox-test, and P < 0.05 was considered statistically significant. The prognostic value of CORO2A in each cancer was determined by Cox regression analysis and Kaplan-Meier survival analysis. The correlation between two variables was calculated by Spearman's test, and P < 0.05 was considered significant. All statistical analyses were conducted using the R software (Version 4.2.1).

3. Results

3.1. CORO2A is expressed in pan-cancer tissues and correlates with clinicopathological indicators

We analyzed the data of 33 cancer types in the UCSC database (Fig. 1A), and found that CORO2A was significantly upregulated in BRCA, cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), cholangiocarcinoma (CHOL), esophageal carcinoma (ESCA), head and neck squamous cell carcinoma (HNSC), kidney renal clear cell carcinoma (KIRC), KIRP, liver hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), PAAD, pheochromocytoma and paranglioma (PCPG), prostate adenocarcinoma (PRAD), thyroid carcinoma (THCA) and uterine corpus endometrial carcinoma (UCEC) tissues compared to the corresponding normal tissues. On the other hand, colon adenocarcinoma (COAD), GBM and KICH tissues expressed significantly lower levels of CORO2A compared to the corresponding normal tissues. The different cancer types were then ranked on the basis of CORO2A expression levels, and the highest and lowest expression was detected in PRAD and KICH respectively (Fig. 1B).

We also analyzed CORO2A levels across the subgroups of age, gender and stage in each tumor type. As shown in Fig. 1C-E, the elderly (age ≥ 65 years) patients with KICH (P < 0.01) and TGCT (P < 0.01), males with HNSC (P < 0.001), and patients with stage ≥ C-E, the elderly (age ≥ 65 years) had higher expression levels of CORO2A, while males with lower grade glioma (LGG, P < 0.05) expressed lower levels.

3.2. CORO2A is prognostically relevant in cancer

The prognostic value of CORO2A in human cancers was determined by Cox analysis and survival analysis. As shown in Fig. 2A-C, CORO2A expression was correlated with the OS in adrenocortical carcinoma (ACC), KIRP, LIHC, PAAD, skin cutaneous melanoma (SKCM) and THCA (all P < 0.05), with the DSS in ACC, bladder urothelial carcinoma (BLCA), GBM, KIRP, LIHC, LUAD, mesothelioma (MESO), PAAD, SKCM and THCA (all P < 0.05), and with the PFS in ACC, KIRP and PAAD (all P < 0.05). Furthermore, high CORO2A expression was associated with shorter OS in BRCA, GBM and PAAD, while low CORO2A levels predicted worse OS in ACC and SKCM (Fig. 2D). Increased expression of CORO2A was also associated with poor DSS in GBM, KIRP and PAAD (Fig. 2E) and a favorable DSS in ACC, BLCA, SKCM and THCA. Finally, the PFS was poor in patients with PAAD expressing high levels of CORO2A, whereas high CORO2A expression correlated with satisfactory PFS in ACC and PCPG (Fig. 2F).

3.3. Differential pan-cancer CORO2A protein expression

In order to estimate the levels of CORO2A protein across multiple cancers, we analyzed the IHC results downloaded from the HPA database. As shown in Fig. 3, CORO2A protein was not detected in the normal breast, brain, kidney and testis tissues, while the corresponding tumor tissues exhibited low staining.
Furthermore, the normal pancreatic tissues were weakly stained for CORO2A, while the tumor tissues showed medium and high staining intensity. Owing to the low protein levels in the tissues, these results deviate considerably from the CORO2A gene expression data from UCSC. Thus, the expression levels of the CORO2A transcript were inconsistent with that of CORO2A protein in tumors due to unknown reasons.

### 3.4. CORO2A expression correlates with genetic instability pan-cancer

The TMB and MSI are important biomarkers of cancer prognoses and therapeutic responses. To this end, we calculated the TMB and MSI of each tumor sample, and analyzed the correlation between CORO2A expression, TMB and MSI in different cancer types (Table 1). As shown in Fig. 4A, the expression level of CORO2A in ACC, BLCA, lymphoid neoplasm diffuse large B-cell lymphoma (DLBCL), HNSC, PAAD, stomach adenocarcinoma (STAD), thymoma (THYM), SKCM and UCEC was significantly correlated with the TMB. Furthermore, CORO2A expression was positively correlated with high mutation frequency in BLCA, HNSC, PAAD, STAD, THYM, SKCM and UCEC, and with low mutation frequency in ACC and DLBCL. We also observed a significant correlation between CORO2A expression and MSI in 5 cancer types, including ACC, BRCA, COAD, DLBCL and SKCM (Fig. 4B). Specifically, CORO2A expression correlated positively with the MSI in ACC, and negatively in BRCA, COAD, DLBCL and SKCM. The MMR genes also influence tumor genesis and progression by regulating genetic instability, whereas DNMTs epigenetically regulate the oncogenes and tumor suppressor genes. Therefore, we analyzed the correlation between CORO2A expression and that of different MMR genes, including MLH1, MSH2, MSH6, PMS2 and EPCAM, across multiple cancers. CORO2A showed a significant association with the MMR genes in all tumor types except ACC, CHOL and MESO (Supplementary Table 1, Fig. 4C). In BLCA, BRCA, CESC, COAD, DLBCL, ESCA, GBM, HNSC, KIRP, LIHC, LUAD, ovarian serous cystadenocarcinoma (OV), PAAD, PCPG, PRAD, rectum adenocarcinoma (READ), SARC, SKCM, TGCT, THYM, UCEC and uterine carcinosarcoma (UCS), CORO2A was positively correlated with all five MMR genes, indicating that CORO2A may regulate the MMR pathways in these tumors. Furthermore, DNMT1, DNMT3A and DNMT3B were significantly correlated with CORO2A expression in 28 cancers, but not in CHOL, acute myeloid leukemia (AML), LGG, MESO and UCS (Supplementary Table 2, Fig. 4D).

Table 1

<table>
<thead>
<tr>
<th>TMB</th>
<th>Relationship between CORO2A gene expression and TMB, MSI in Pan-cancer.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cancer Type</td>
</tr>
<tr>
<td>HNSC</td>
<td>0.164540263</td>
</tr>
<tr>
<td>PAAD</td>
<td>-0.280738719</td>
</tr>
<tr>
<td>ACC</td>
<td>0.35332292</td>
</tr>
<tr>
<td>STAD</td>
<td>0.16226273</td>
</tr>
<tr>
<td>UCEC</td>
<td>0.114510238</td>
</tr>
<tr>
<td>KICH</td>
<td>0.322916734</td>
</tr>
<tr>
<td>DLBCL</td>
<td>0.376481745</td>
</tr>
<tr>
<td>THYM</td>
<td>0.192093663</td>
</tr>
<tr>
<td>BLCA</td>
<td>0.098084145</td>
</tr>
</tbody>
</table>

### 3.5. CORO2A expression is associated with the tumor immune microenvironment

The ESTIMATE algorithm was used to calculate the stromal and immune cell scores in 33 types of cancer, and their correlation with CORO2A expression levels were analyzed (Supplementary Table 3). As shown in Fig. 5A, high CORO2A expression correlated positively with the stromal scores in GBM, KICH and KIRP, and negatively in PAAD. In addition, high CORO2A expression also showed a significant positive correlation with immune scores in KIRP and a negative correlation in BRCA, PRAD and TGCT (Fig. 5B). The correlation between CORO2A expression and the stromal and immune scores in other cancers is shown in Supplementary Fig. 1.

We then conducted gene co-expression analyses using TISIDB data to explore the correlation between CORO2A and IRGs in 33 tumors. The analyzed IRGs encoded immunosuppressive, immunostimulatory and MHC proteins. As shown in the heatmaps in Fig. 6, almost all IRGs were co-expressed with CORO2A. Among the immunosuppressive genes, TGFB1 showed the most significant positive correlation with CORO2A in THCA, while LGALS9 was negatively correlated with CORO2A in PRAD (Fig. 6A). Furthermore, CORO2A and the immune activation gene CD276 were positively correlated in THCA, while CORO2A and C10orf54 showed a significant negative correlation in PRAD (Fig. 6B). The MHC molecule TAPBP also showed a significant positive correlation with CORO2A in UCS, while a negative correlation was observed between CORO2A and HLA-DMA in PRAD (Fig. 6C).

To further assess the potential correlation between CORO2A expression and immune cell infiltration, we classified twelve cancer types as low-risk and high-risk malignancies depending on the prognostic role of CORO2A. Thus, BRCA, GBM, KICH, KIRP, PAAD and TGCT were classified as high-risk since CORO2A is a potential risk factor for these cancers. On the other hand, ACC, COAD, READ, SKCM, STAD and THCA were classified as low-risk on account of the protective role of CORO2A in these cancers. The infiltration levels of 22 immune cells in these tumors were analyzed using the CIBERSORT algorithm. As shown in Table 2, CORO2A expression was significantly correlated with the infiltration of multiple immune cell types in BRCA (n = 11), GBM (n = 6), KICH (n = 2), KIRP (n = 8), PAAD (n = 4) and TGCT (n = 5). Furthermore, the number of infiltrating immune cells was greater in the high-risk cancers compared to the low-risk cancers.
Table 2  
Association between CORO2A gene expression and immune cell infiltration in different cancers.

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>High-risk cancer (P-value/Cor)</th>
<th>Low-risk cancer (P-value/Cor)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BRCA GBM KICH KIRP PAAD TGCT</td>
<td>ACC COAD READ SKCM STAD THCA</td>
</tr>
<tr>
<td>B cells naive</td>
<td>*/-0.07 -0.099 -0.160 -0.030</td>
<td>*/-0.17 ***/-0.36 0.210 0.032 0.090 0.034 0.015 0.100</td>
</tr>
<tr>
<td>Dendritic cells activated</td>
<td>***/-0.20 0.000 -0.170 -0.037</td>
<td>0.069 0.000 */-0.34 0.042 0.130 */-0.11 -0.013 ***/-0.14</td>
</tr>
<tr>
<td>Dendritic cells resting</td>
<td>***/-0.08 0.000 0.160 */-0.14</td>
<td>0.099 0.130 0.240 -0.047 -0.065 0.026 -0.040 ***/-0.30</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0.000 -0.150 -0.011 0.000</td>
<td>0.000 0.000 */-0.43 -0.003 -0.064 0.000 -0.005 0.000</td>
</tr>
<tr>
<td>Macrophages M0</td>
<td>***/-0.11 ***-/0.34 0.300 0.048</td>
<td>0.140 0.063 -0.210 */-0.11 -0.082 0.060 ***/-0.23 0.060</td>
</tr>
<tr>
<td>Macrophages M1</td>
<td>0.016 */-0.18 0.180 */-0.15 0.039 */-0.21 0.230 */-0.12 -0.024 -0.031 -0.087 -0.098</td>
<td></td>
</tr>
<tr>
<td>Macrophages M2</td>
<td>***/-0.11 0.094 -0.130 */-0.15 -0.059 ***/-0.40 -0.063 ***/-0.17 -0.092 ***/-0.14 */-0.12 -0.074</td>
<td></td>
</tr>
<tr>
<td>Mast cells activated</td>
<td>0.000 */-0.19 -0.110 0.000 0.000</td>
<td>0.000 -0.190 -0.072 -0.084 0.078 0.016 0.000</td>
</tr>
<tr>
<td>Mast cells resting</td>
<td>***/-0.23 -0.120 -0.021 0.026</td>
<td>0.042 0.140 0.160 0.087 0.100 -0.037 -0.071 ***/-0.16</td>
</tr>
<tr>
<td>Monocytes</td>
<td>0.307 ***/-0.23 -0.270 ***/-0.26 ***/-0.21 0.150 -0.170 ***/-0.15 -0.021 -0.036 ***/-0.25 -0.029</td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>0.000 0.110 0.170 ***/-0.21 -0.110 0.000 0.110 */-0.1  */-0.16 0.091 0.040 0.000</td>
<td></td>
</tr>
<tr>
<td>NK cells activated</td>
<td>***/-0.10 0.045 -0.140 ***/-0.16 -0.076 */-0.18 -0.110 -0.031 0.011 0.022 -0.026 -0.002</td>
<td></td>
</tr>
<tr>
<td>NK cells resting</td>
<td>0.000 -0.021 -0.270 0.000 0.075</td>
<td>0.000 0.077 0.063 -0.033 0.026 */-0.12 -0.043</td>
</tr>
<tr>
<td>Plasma cells</td>
<td>-0.022 -0.036 0.270 ***/-0.18 0.041 */-0.20 */-0.38 ***/-0.28 0.066 0.042 -0.029 */-0.12</td>
<td></td>
</tr>
<tr>
<td>T cells CD4 memory activated</td>
<td>***/-0.16 0.110 0.000 0.000</td>
<td>-0.084 -0.090 0.037 -0.002 -0.093 0.008 -0.056 0.000</td>
</tr>
<tr>
<td>T cells CD4 memory resting</td>
<td>***/-0.16 ***/-0.30 -0.015 -0.120 ***/-0.23 -0.044 0.140 ***/-0.17 */-0.17 0.019 ***/-0.19 0.070</td>
<td></td>
</tr>
<tr>
<td>T cells CD8</td>
<td>***/-0.13 */-0.18 0.240 0.110 ***/-0.20 -0.091 0.230 -0.032 -0.130 -0.023 ***/-0.19 ***/-0.19</td>
<td></td>
</tr>
<tr>
<td>T cells follicular helper</td>
<td>***/-0.11 0.013 */-0.37 ***/-0.17 -0.110 -0.059 0.094 -0.039 0.035 0.024 0.015 -0.044</td>
<td></td>
</tr>
<tr>
<td>T cells gamma delta</td>
<td>0.051 0.000 -0.150 0.000 0.000</td>
<td>0.000 0.230 0.000 0.000 -0.043 0.000 0.000</td>
</tr>
<tr>
<td>T cells regulatory (Tregs)</td>
<td>0.000 0.057 ***/0.51 -0.006 0.078 -0.091 0.230 0.058 0.033 -0.086 ***/0.14 */-0.12</td>
<td></td>
</tr>
</tbody>
</table>

Annotation: BRCA, breast invasive carcinoma; GBM, glioblastoma multiforme; KICH, kidney chromophobe; KIRP, kidney renal papillary cell carcinoma; PRAD, prostate adenocarcinoma; TGCT, testicular germ cell tumors; ACC, adrenal cortical carcinoma; COAD, colon adenocarcinoma; READ, Rectum adenocarcinoma; SKCM, skin cutaneous melanoma; STAD, stomach adenocarcinoma; THCA, thyroid carcinoma.

Cor, R value of Spearman's correlation.

* P < 0.05.

** P < 0.01.

*** P < 0.001.

CORO2A expression correlated positively with infiltrating naive B cells in BRCA, and negatively in PAAD and TGCT (Fig. 7A). The activated dendritic cells (DCs) showed a negative correlation with CORO2A expression in BRCA (Fig. 7B). In BRCA and KIRP, the levels of resting DCs were positively correlated to CORO2A expression (Fig. 7C). The M0 macrophages in BRCA and GBM respectively showed negative and positive correlation with CORO2A expression (Fig. 7D), and the M1 macrophages were positively correlated to CORO2A in KIRP and TGCT, and negatively in GBM (Fig. 7F). On the other hand, the M2 macrophages presented a positive correlation with CORO2A expression in BRCA and TGCT, but a negative correlation in KIRP (Fig. 7H). In addition, CORO2A was positively correlated with the activated mast cells in GBM (Fig. 7E), and with the resting mast cells in BRCA (Fig. 7G). CORO2A expression was positively correlated with...
the neutrophils in KIRP (Fig. 7I), and with the activated CD4 memory T cells in BRCA (Fig. 7J). The infiltration of monocytes was negatively correlated with CORO2A in GBM, KIAP and PAAD (Fig. 7K), while that of regulatory T cells (Tregs) was positively correlated in KICH (Fig. 7L). A negative correlation was observed between the activated NK cells and CORO2A in BRCA and KIRP, and a positive correlation was observed in TGCT (Fig. 7M). CORO2A expression had a positive correlation with the plasma cells in KIRP, and a negative correlation in TGCT (Fig. 7N). The resting CD4 memory T cells were positively correlated with CORO2A expression in BRCA and PAAD, but negatively correlated in GBM (Fig. 7O). The CD8 T cells on the other hand were negatively correlated with CORO2A in BRCA and PAAD, and positively in GBM (Fig. 7P). Finally, CORO2A expression was positively correlated with the T follicular helper cells in KICH and KIRP (Fig. 7Q).

3.6. Pan-cancer association of CORO2A with immune subtypes, pathways and drug sensitivity

We analyzed the relationship between CORO2A and six immune subtypes, including wound healing, IFN-γ dominant, inflammatory, lymphocyte depleted, immunologically quiet and TGF-β dominant, in 33 tumors and found that CORO2A expression was significantly correlated to these immune subtypes in BRCA, KICH, KIRC, KIRP, LUAD, LUSC, OV, PRAD, SARC and STAD (Supplementary Fig. 2).

GO functional annotation and KEGG pathway analysis of CORO2A were performed for the six prognosis-related tumors. CORO2A positively regulated biological process of gland development, cell cycle phase transition, cellular amide metabolic and extracellular matrix in TGCT. In addition, CORO2A was also positively correlated to several immune-related functions in GBM, KICH and KIRP, including humoral immune response, immune response regulation signaling pathway, leukocyte migration, regulation of lymphocyte activation, antigen receptor mediated signaling pathway, B cell activation and regulation of cytokine production (Fig. 8A). KEGG pathway analysis indicated that CORO2A positively regulates several immune-related pathways, such as antigen processing and presentation, cytokine receptor interaction, neuroactive ligand receptor interaction, systemic lupus erythematosus and T cell receptor signaling pathway. In contrast, CORO2A negatively regulates RNA degradation in KICH and the Toll like receptor signaling pathway in PAAD (Fig. 8B).

Finally, the drug sensitivity analysis revealed that tumors with high CORO2A expression are sensitive to perifosine, chelerythrine and palbociclib, but resistant to everolimus, bleomycin, and LY294002 (Supplementary Fig. 3).

4. Discussion

CORO2A is a member of the coronin family and makes up the N-CoR complex. In humans, the coronin family is composed of seven proteins containing WD-repeat domains that regulate actin-based cellular processes. Recent studies have shown that the expression level of CORO2A in BRCA and OSCC correlates with tumor proliferation, invasion and migration. To better understand the role of CORO2A in different cancers, we analyzed the pan-cancer expression patterns of CORO2A, as well as its relationship with the clinical parameters, prognostic indicators and immune landscape in these cancers. Our findings indicated that CORO2A is prognostically significant in BRCA, GBM, KICH, KIRP, PAAD and TGCT, and its functions and pathways in these malignancies were further explored through GSEA.

Analysis of 33 cancer data sets from UCSC showed that CORO2A was upregulated in the BRCA, CESC, CHOL, ESCA, HNSC, KIRC, KIRP, LIHC, LUAD, LUSC, PAAD, PCPG, PRAD, THCA and UCEC tissues compared to the corresponding normal tissues. On the other hand, COAD, GBM and KICH tissues expressed significantly lower levels of CORO2A compared to the corresponding para-cancerous or normal tissues. We also analyzed CORO2A levels according to age, gender and stage, and detected higher expression in KICH and TGCT patients aged ≥ 65 years, males with HNSC, and in stage ≥ TGCT and THCA. In contrast, males with LGG had lower CORO2A levels. The differential expression of CORO2A is indicative of its potential role in multiple cancers, either as an oncogene or as a tumor suppressor, and may help guide therapy based on age, gender and tumor stage.

High CORO2A expression correlated to worse OS in BRCA, GBM and PAAD, and favorable OS in ACC and SKCM. Furthermore, increased expression levels of CORO2A were associated with poor DSS in GBM, KIRP and PAAD, and favorable DSS in ACC, BLCA, SKCM and THCA. Elevated CORO2A also predicted poor PFS in PAAD, and a satisfactory PFS in ACC and PCPG. Thus, CORO2A is a promising prognostic biomarker in various cancers, and CORO2A protein expression was confirmed in six tumor types.

TMB is a pan-cancer prognostic biomarker, and has been known to predict the response to immunotherapy [23, 24] in non-small-cell lung and colorectal cancers [25, 26]. Furthermore, TMB can also predict prognosis after immunotherapy in pan-cancer patients [27]. MSI is also an important predictive biomarker for immune-checkpoint blockade therapy [28, 29]. For instance, a high frequency of MSI in colorectal cancer is an independent predictor of clinical characteristics and prognosis [30, 31]. Various MMR genes have been identified that rectify DNA replication errors and ensure the stability of the genome [32, 33]. An aberrant MMR system increases the frequency of mismatches, insertions and other mutations in microsatellite sequences, thereby increasing the risk of genomic instability, mutant phenotypes and tumorigenesis [34, 35]. Abnormal DNA hypemethylation is also common in all stages of tumor genesis and development, and overexpression of DNMT has been observed in the precancerous lesion stage. This suggests that DNMT overexpression and activation, and the subsequent hypermethylation-induced silencing of various tumor suppressor genes is one of the early molecular events in tumor genesis and development [36, 37]. Furthermore, DNMT is closely related to the clinicopathological features and prognosis of cancer patients [38, 39]. In this study, we found that CORO2A expression correlated significantly with the TMB in 9 cancers, and with MSI in 5 cancers. Based on existing research and our findings, we hypothesize that tumors overexpressing CORO2A, and with a high TMB and MSI may have a better prognosis after immunotherapy where CORO2A expression is positively correlated with TMB. In addition, CORO2A expression was positively correlated to MMR genes in 30 cancers including BRCA, GBM, KICH, KIRP, PAAD and TGCT, and with the three DNMTs in 28 cancers including GBM, KICH, KIRP and TGCT. Taken together, it is reasonable to surmise that CORO2A plays an important role in MMR and the epigenetic regulation of cancer-related genes via DNA methylation, and its expression level in tumor tissues can be used as a marker to identify suitable patients for immunotherapy.
The tumor microenvironment (TME) consists of the malignant cells, immune cells, stromal cells and other populations, and plays an essential role in tumor genesis and progression [40, 41]. Furthermore, the IRG expression profile is a reliable prognostic signature in cancer since it is associated with tumor cell proliferation, cell-mediated immunity and tumorigenic signaling pathways [42–47]. We found CORO2A expression was significantly correlated with both the stromal and immune components in BRCA, GBM, KICH, KIRP, PAAD and TGCT. In addition, almost all IRGs analyzed in our study, including those encoding immunosuppressive, immunostimulatory and MHC molecules, were co-expressed with CORO2A. Furthermore, the CORO2A expression levels in different cancers correlated with the infiltration of multiple immune cell populations, which significantly impact tumor occurrence and development [48]. Some studies have associated tumor-infiltrating B cells with a favorable disease outcome [49], whereas one report indicates that B cell infiltration in metastatic ovarian carcinoma portends poor outcomes [50]. Mature DCs are associated with favorable immune infiltration and improved prognosis in patients with ovarian cancer [51]. Insufficient crosstalk between the antigen presenting DCs and the anti-tumor effector T cells is one of the main mechanisms of immune tolerance in HCC tumors [52]. Macrophages play a key role in cancer-associated inflammation, which is a direct causal factor in the initiation, progression and metastasis of breast as well as head and neck tumors [53–55]. The immune checkpoint blockers that are currently used to activate T cells in cancer patients (such as anti-PD-1 antibodies) may also target NK cells [56]. Coffelt et al have reported that neutrophils expand in the TME and are generally related to poor prognosis in patients with solid tumors [57]. Furthermore, mast cells actively contribute to neovascularization of tumors by releasing classical proangiogenic factors such as VEGF, FGF-2, PDGF and IL-6, as well as the non-classical proangiogenic factors including tryptase and chymase into the tumors [58]. Monocytes are the bridge between innate and adaptive immune responses, and are known to induce immune tolerance, angiogenesis and metastasis of tumor cells. On the other hand, monocytes can also activate anti-tumor effectors and antigen-presenting cells [59]. The degree of T cell infiltration in tumor tissues is an independent marker of favorable prognosis in several human malignancies [60]. Maartje and Brad reviewed studies with cohorts of 50 or more cancner patients, and found that tumor-infiltrating CD8+ T cells and plasma cells correlated positively with anti-tumor immunity [61]. The CD4+ T cells augment the function of CD8+ T cells during the primary immune response [62], and have been associated with better outcomes of cancer immunotherapies [63]. In addition to the CD8+ T cells, the CD4+ T cells can also stimulate the NK cells and other innate immune cell types [64]. Regulatory T cells or Tregs are an immunotolerant subset that repress autoreactive T cells [63], whereas the T follicular helper (Th) cells activate B cell-mediated antibody responses and their presence in solid tumors is often correlated with a better therapeutic outcomes [65]. Our findings indicate that CORO2A may play a crucial role in the recruitment and regulation of multiple immune cells in the tumors, and thus affect patient prognosis. The results of GSEA further showed that CORO2A positively regulates immune-related function and pathways, such as humoral immune response, immune response regulation signaling pathway, leukocyte migration, regulation of lymphocyte activation, antigen receptor-mediated signaling pathway, B cell activation, antigen processing and presentation, systemic lupus erythematosus and T cell receptor signaling pathways, which underscored its role as a prognostic biomarker of cancer immunotherapy.

Our study has some limitations that ought to be considered. First, the data used in the study were retrieved from the UCSC database and not validated in other independent datasets. Second, numerous microarray and sequencing data were gathered by analyzing cancer tissue information. Therefore, analysis of immune cell markers at the cellular level may lead to systematic bias. In order to solve this issue, more detailed research should be further carried out. It is possible that single-cell RNA sequencing data will be used. Third, we mainly focused on the bioinformatics data, and did not validate the findings through in vivo and in vitro experiments. The cellular and molecular mechanisms underlying the function of CORO2A in cancers remain to be elucidated. Fourth, although CORO2A expression in the tumor tissues was correlated to immune cell infiltration and patient survival, we were unable to confirm whether CORO2A may affect patient survival across immune infiltration. Future prospective studies looking at CORO2A expression and immune cell infiltration in different cancer populations may provide mechanistic insights.

5. Conclusions

In summary, CORO2A was related to the disease prognosis and correlated with immune infiltration in pan-cancers, particularly in BRCA, GBM, KICH, KIRP, PAAD, and TGCT. Moreover, CORO2A expression was associated with TMB, MSI, MMR, DNMTs, and immune cell content in various cancer types. As such, CORO2A may serve as a prognostic biomarker in pan-cancer. These findings may provide an immune-based anti-tumor strategy involving the energy system of either tumor cells or tumor microenvironment infiltrates.

Declarations

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Authors’ contributions

M. X and P. W. wrote the manuscript text and put forward the idea of the article. D. Z. and X. W. contributed to completing the picture modification. E. C. and X. D. completed the revision and review of the article.

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Availability of data

All data were from UCSC (https://xena.ucsc.edu/), HPA (https://www.proteinatlas.org/), TIMER (https://cistrome.shinyapps.io/timer/), TISIDB (http://cis.hku.hk/TISIDB/), and GSEA (http://www.gsea-msigdb.org/gsea/msigdb/index.jsp) databases, which are publicly available.
Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable

Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References


Figures

(A) Differential expression of CORO2A in normal tissues and tumor tissues. (B) CORO2A expression in 33 types of cancer. (C-E) Association of CORO2A expression with age, gender, and clinical stage in pan-cancer.

Figure 1

The expression of CORO2A in pan-cancer. (A) Differential expression of CORO2A in normal tissues and tumor tissues. (B) CORO2A expression in 33 types of cancer. (C-E) Association of CORO2A expression with age, gender, and clinical stage in pan-cancer.
Figure 2

The prognostic value of CORO2A in human cancers using Cox analysis and Kaplan-Meier method. **(A-C)** The effect of CORO2A on overall survival (OS), disease-specific survival (DSS), and progression-free survival (PFS) in 33 types of cancers using Cox proportional hazards model. **(D-F)** The survival curve of CORO2A for OS, DSS, and PFS in various cancers using Kaplan-Meier methods and the log-rank test. Values of $P < 0.05$ were considered and displayed.
Figure 3

Immunohistochemistry images in normal and tumor tissues. CORO2A protein expression was significantly higher in Breast invasive carcinoma (BRCA), Glioblastoma multiforme (GBM), Kidney Chromophobe cell carcinoma (KICH), Kidney renal papillary cell carcinoma (KIRP), Pancreatic adenocarcinoma (PAAD), and Testicular Germ Cell Tumors (TGCT) tissues than normal tissues. (A) BRCA. (B) GBM. (C) KICH, KIRP. (D) PAAD. (E) TGCT.
Figure 4

The correlations between CORO2A expression and tumor mutation burden (TMB), microsatellite instability (MSI), mismatch repair (MMR) genes, and DNA methyltransferase (DNMTs) in various cancers. (A) The correlation between CORO2A expression and TMB in 33 types of cancers. (B) The correlation between CORO2A and MSI in 33 types of cancers. (C) The correlation between CORO2A and five MMR genes in 33 types of cancers. (D) The correlation between CORO2A and three methyltransferases in 33 types of cancers.

Figure 5
Association between CORO2A expression and the tumor microenvironment in six tumors. (A) Association between CORO2A and stromal scores in Breast invasive carcinoma (BRCA), Glioblastoma multiforme (GBM), Kidney Chromophobe cell carcinoma (KICH), Kidney renal papillary cell carcinoma (KIRP), Pancreatic adenocarcinoma (PAAD), and Testicular Germ Cell Tumors (TGCT). (B) Association between CORO2A and immune scores in BRCA, GBM, KICH, KIRP, PAAD, and TGCT.

Figure 6

Co-expression of CORO2A and immune-related genes. (A) Co-expression of CORO2A and immunosuppressive genes, and the scatter diagram with the highest positive and negative correlation. (B) Co-expression of CORO2A and immune activation genes, and the scatter diagram with the highest positive and negative correlation. (C) Co-expression of CORO2A and MHC-molecule, and the scatter diagram with the highest positive and negative correlation.
Figure 7

Relationship between CORO2A expression and infiltrating levels of immune cells in pan-cancer. CORO2A expression has significant correlation with infiltrating levels of B cells naive in BRCA, PAAD, and TGCT (A), dendritic cells activated in BRCA (B), dendritic cells resting in BRCA and KIRP (C), Macrophages M0 in BRCA and GBM (D), mast cells activated in GBM (E), Macrophages M1 in GBM, KIRP, and TGCT (F), resting mast cells in BRCA (G), Macrophages M2 in BRCA, KIRP and TGCT (H), neutrophils in KIRP (I), T cells CD4 memory activated in BRCA (J), monocytes in GBM, KIRP, and PAAD (K), T cells regulatory (Tregs) in KICH (L), NK cells activated in BRCA, KIRP, and TGCT (M), plasma cells in KIRP and TGCT (N), T cells CD4 memory resting in BRCA, GBM, and PAAD (O), T cells CD8 in BRCA, GBM, and PAAD (P), T cells follicular helper in KICH and KIRP (Q). Positive R-value indicates a positive correlation between CORO2A gene expression and infiltrating levels of immune cells, while a negative R-value means a negative correlation. Breast invasive carcinoma (BRCA), Glioblastoma multiforme (GBM), Kidney Chromophobe cell carcinoma (KICH), Kidney renal papillary cell carcinoma (KIRP), Pancreatic adenocarcinoma (PAAD), and Testicular Germ Cell Tumors (TGCT).

Figure 8

Pathway analysis of CORO2A in six cancers. (A) GO functional annotation of CORO2A in six prognosis-related tumors. (B) KEGG pathway analysis of CORO2A in six prognosis-related tumors. Values of $P < 0.05$ and results higher than 5 were considered and displayed.
Supplementary Files

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