Role of SERCA3 in the Prognosis and Immune Function in Pan-Cancer

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The sarcoplasmic reticulum calcium adenosine triphosphatase (ATPase) 3 (SERCA3), a member of the SERCA protein family, is located at the endoplasmic reticulum. Its main function is to pump Ca2+ into the endoplasmic reticulum and is involved in maintaining intracellular calcium homeostasis and signal transduction, which are very important factors impacting cancer development and progression. However, the specific role of SERCA3 in cancer remains unclear. Our study, for the first time, comprehensively analyzed the SERCA3 expression profile in multiple cancers and its prognostic value in different cancers using bioinformatics. Furthermore, TCGA database was applied to evaluate the certain correlation of SERCA3 expression with immune modulator genes, immune checkpoints, immune cell infiltration, TMB, and MSI. The results revealed that in many cancers, SERCA3 expression was markedly decreased, which was related to poor prognosis. Additionally, we noticed that SERCA3 expression was correlated with TNM classification and WHO cancer stages in some cancer types. The Pearson correlation analysis showed that SERCA3 expression was closely associated with chemokines, chemokine receptors, MHC, immune activation genes, and immunosuppressive genes. In most cancer types, SERCA3 expression was also associated with immune checkpoints, including PD-CD1 and CTLA-4. Further analysis suggested that SERCA3 was significantly correlated with CD8+ T cells, and regulatory T cells. Additionally, pan-cancer analysis confirmed that SERCA3 expression was related to TMB and MSI. In conclusion, these results offer a new insight into the functions and effects of SERCA3 in pan-cancer, and further provide some basis for considering SERCA3 as a potential cancer treatment target and biomarker.

1. Introduction

Cancer, a major cause of death worldwide, imposed a heavy burden on society [1–4]. Cancer incidence and mortality are exceptionally high. Global cancer cases increased by 19 million in 2020, and nearly 10 million deaths due to cancer were recorded. Furthermore, America cancer cases expected to rise by 1.9 million, and new cancer deaths are expected to reach 60,936 by 2022 [3, 5]. The rapid development of cancer immunotherapy in recent years has improved the prognosis of some cancer patients; however, immune checkpoint inhibitors have not achieved satisfactory results in most cancer cases [6–8]. This may be attributed to the susceptibility of cancer to mutations and drug resistance, which significantly limit cancer screening and treatment [9, 10]. Therefore, identifying new therapeutic targets or biomarkers is important for the early screening and successful treatment of cancer.
The sarcoplasmic reticulum calcium adenosine triphosphatase (ATPase) 3 (SERCA3) enzyme belongs to the SERCA protein family and is found in the endoplasmic reticulum. It pumps calcium ions (Ca$^{2+}$) from the cytoplasm into the endoplasmic reticulum, which is the main calcium-storing organelle. In most cells, it is mainly involved in maintaining homeostasis of endoplasmic reticulum Ca$^{2+}$ and the intracellular Ca$^{2+}$ concentration [11–13]. Being the second messenger of intracellular signal transduction, Ca$^{2+}$ is an important regulator of cellular signaling activities, and intracellular Ca$^{2+}$ disorders can affect gene expression, proliferation, differentiation, and cell death [14–16]. Cumulative evidence suggests that Ca$^{2+}$ signal transduction is crucial for cancer development. The growth, proliferation, invasion, death, and drug resistance of cancer cells are regulated by Ca$^{2+}$ [17–20]. It has been reported that abnormal changes in amplitude of cytoplasmic free Ca$^{2+}$ concentration and duration of Ca$^{2+}$ elevation may promote breast cancer cell proliferation and invasion [17, 21]. The same phenomenon was confirmed in endometrial and colorectal cancers [22, 23].

Intracellular calcium homeostasis is a crucial factor that affects the occurrence and development of cancers. SERCA3 is one of the most important calcium modulators involved in maintaining intracellular calcium homeostasis by modulating the entry of cytoplasmic calcium into the endoplasmic reticulum. However, no pan-cancer study of SERCA3 has been reported, and the role of SERCA3 in pan-cancer remains unknown. Our study elucidated the SERCA3 expression profile and examined correlations between SERCA3 expression and cancer prognosis; moreover, the correlation between SERCA3, tumor-node-metastasis (TNM) classification, and World Health Organization (WHO) cancer stages was also detected. The relationship between SERCA3 with immune modulator pathways, immune checkpoints, and immune cell infiltration levels was analyzed. Finally, we examined the correlation of SERCA3 expression with cancer mutation burden (TMB) and microsatellite instability (MSI). We provided a study of SERCA3 in pan-cancer, focusing on the role of SERCA3 in cancer immune functions and the potential mechanisms of cancer immunotherapy.

2. Materials and Methods

2.1. SERCA3 Expression in Human Pan-Cancer. The Cancer Genome Atlas (TCGA) pan-cancer database (PANCAN, N = 10535, G = 60499, year: updated in 2022) was downloaded from the UCSC Cancer Genome Browser (https://xenabrowser.net/), from which SERCA3 expression data for each cancer type were extracted [24, 25]. Furthermore, we screened data from the Primary Tumor (year: updated in 2022) and Solid Tissue Normal (year: updated in 2022) databases to compare SERCA3 expression between different cancer types. The final cancer expression data were obtained after eliminating cancer types from less than three sample. All expression data were standardized by log2 conversion. SERCA3 expression in different cancers was calculated using R software (version 3.6.4) [24]. Additionally, we used the Human Protein Atlas (HPA) database to investigate SERCA3 expression in normal and cancer tissues in humans.

2.2. Association of SERCA3 Expression with TNM Classification and WHO Cancer Stages. We selected SERCA3 expression data from TCGA-LAML (year: updated in 2022) and Primary Tumor databases. The final cancer expression data were obtained after eliminating cancer types from less than three sample. Using R software to correlate SERCA3 expression with TNM classification and WHO cancer stages in various types of cancer. All expression data were standardized via log2 conversion.

2.3. Prognostic Analysis. In addition to extraction of data from TCGA-LAML, TCGA-SKCM (year: updated in 2022), and Primary Tumor databases, prognostic data for TCGA within 1 month of follow-up were also obtained from a previously published TCGA prognosis study [26], and pan-cancer data were obtained after eliminating the cancer types with less than 10 samples. Applying hazard ratios (HR) and 95% confidence intervals (CI) to assess overall survival (OS).

2.4. Relationship between SERCA3 Expression and Immune Modulator Pathways and Immune Checkpoints. The SERCA3 expression data and data on five immune modulator pathways, including chemokines, chemokine receptors, major histocompatibility complex (MHC), immune activation genes, and immunosuppressive genes, were extracted from TCGA. Further, we excavated TCGA-LAML and Primary Tumor data and plotted the Spearman correlation analysis heat map of SERCA3 expression and five immune modulator pathways.

Moreover, we extracted expression data on two immune checkpoints, including 24 immune checkpoint inhibitors and 36 immune checkpoint stimulators, from a previous study [27]. We screened the cancer samples as follows: TCGA-LAML and Primary Tumor. All expression data were standardized by log2 conversion. The Pearson correlation between SERCA3 level and two immune checkpoint pathways was calculated.

2.5. SERCA3 Expression and Immune Cell Infiltration. Mapping the obtained SERCA3 expression data of each cancer type to Gene Symbol, using CIBERSORT [28, 29] in R software IOBR (version 0.99.9) [30]. Immune cell infiltration levels of each cancer type were assessed, the corr.test function of the R software psych (version 2.1.6) was used to calculate the Spearman correlation coefficient.

2.6. Association of SERCA3 Expression with TMB and MSI. SERCA3 expression and TMB data were extracted from TCGA and Primary Tumor. Downloaded TCGA level 4 simple nucleotide variation data processed by MiTect2 software from GDC [31]. TMB for each cancer type was estimated using the “maftools” R package (version 2.8.05). Subsequently, SERCA3 expression and TMB data were integrated. The final cancer expression data were obtained after eliminating cancer types from less than three sample. All expression data were standardized via log2 conversion.
Spearman’s correlation between SERCA3 expression and TMB was then compared. Subsequently, we obtained the MSI score of each cancer type from a previous study [32], and the MSI score and SERCA3 expression data were integrated; less than three type from a previous study [32], and the MSI score and TMB was then compared.

2.7. Statistical Analysis. Differential expression of SERCA3 in various cancer types was evaluated using Student’s t-test. Kruskal–Wallis test and Mann–Whitney U-test were used to calculate the relationship of SERCA3 expression with TNM classification and WHO cancer stages. HR and p-values for overall survival were assessed using the log-rank test. Spearman correlation and Pearson’s correlation were applied to detect the correlation between SERCA3 expression and immunity. All analyses were performed using R software (IOBR, psych, and maftools). \( p \leq 0.05 \) was considered a statistically significant difference.

3. Results

3.1. SERCA3 Expression in Human Pan-Cancer. We calculated SERCA3 expression in various cancer types based on TCGA database. The results showed inconsistent expression of SERCA3 in different types of cancer; it had significantly low expression in 13 cancers, including GBM, GBMLGG, LGG, COAD, COADREAD, KIRP, KIPAN, PRAD, LUSC, THCA, READ, BLCA, and KICH. Contrastingly, two cancers, including BRCA and CHOL, showed significantly high SERCA3 expression (Figure 1). Immunohistochemistry (IHC) of SERCA3 in COAD, PRAD, LUSC, and THCA supported this view (Figure 2). These cancer abbreviations are defined in Supplement 1.

3.2. Association of SERCA3 Expression with TNM Classification and WHO Cancer Stages. To understand the association of SERCA3 expression with TNM classification and WHO cancer stage, we measured SERCA3 expression among the different TNM classification. Strong association of SERCA3 expression with TNM classification was found in KIRP \((p = 0.01)\), GBMLGG \((p = 0.02)\), LGG \((p = 0.02)\), and COADREAD \((p = 0.05)\) (Figure 3(a)). Subsequently, the expression of SERCA3 in the WHO cancer stages was assessed based on the Union for International Cancer Control definition. SERCA3 expression was downregulated in some advanced-stage cancers, including GBMLGG \((p = 1.5e-3)\), BRCA \((p = 0.05)\), LGG \((p = 0.04)\), and GBM \((p = 0.02)\) (Figure 3(b)).

3.3. Prognostic Analysis of SERCA3 Expression. The relevance between the expression of SERCA3 and the OS in cancer patients was evaluated. SERCA3 is a protective factor in most cancers, HR and 95%CI for cancers were PAAD \((0.68, 0.56–0.81)\), CESC \((0.85, 0.72–0.99)\), SKCM \((0.86, 0.80–0.93)\), SARC \((0.81, 0.71–0.92)\), BLCA \((0.89, 0.80–0.98)\), SKCM-M \((0.87, 0.80–0.95)\), COADREAD \((0.80, 0.69–0.94)\), HNSC \((0.87, 0.79–0.95)\), KIRC \((0.87, 0.75–0.99)\), COAD \((0.83, 0.70–0.99)\), OV \((0.92, 0.84–1.00)\), while SERCA3 is an adverse factor in KIPAN \((1.11, 1.00–1.22)\), GBMLGG \((1.53, 1.38–1.70)\), TGCT \((3.20, 0.94–10.88)\), UVM \((2.04, 1.39–3.01)\), LGG \((1.53, 1.33–1.76)\). The pan-cancer results were then used to perform regression analysis (Figure 4).

3.4. Relationship between SERCA3 Expression and Immune Modulator Pathways and Immune Checkpoints. Based on TCGA database, we analyzed the connection between SERCA3 expression and the five immune modulator pathways. The heat map revealed that SERCA3 expression was closely correlated with the level of chemokines and chemokine receptors, such as CCL5, CCL17, CCL22, CCR4, and CCR5 (Figures 5(a) and 5(b)). Furthermore, SERCA3 expression was closely correlated with MHC, immune activation genes, and immunosuppressive genes such as HLA-DRB1, HLA-E, PDCD1 (PD-1), TGF-B1, CTLA-4, TIGIT, and ICOS in most cancer types (Figures 5(c)–5(e)).

Immunotherapy is increasingly becoming an important means of cancer treatment, the application of immune checkpoint inhibitors has improved the prognosis of some cancer patients [33, 34]. Therefore, we collected the expression data of 60 common immune checkpoints [27], using Pearson’s correlation analyzed the relationship between SERCA3 expression and immune checkpoints. Our results suggested that in most types of cancer, SERCA3 expression was distinctly related to immune checkpoints, such as TLR4, ICOS, CTLA-4, PDCD1, and CD27 (Figure 6).

3.5. Immune Cell Infiltration Analysis. The abundances of 22 immune cells were calculated using CIBERSORT, the relationship between SERCA3 expression and immune cell infiltration levels in different cancer types was analyzed. We noticed that the abundance of many immune cells was correlated with SERCA3 expression. SERCA3 expression was positively connected with CD8+ T cells, regulatory T (Treg) cells, M1 macrophages, and naïve B cells, while negatively correlated with M0 macrophages, M2 macrophages, and eosinophils (Figure 7).

3.6. Association of SERCA3 Expression with TMB and MSI. TMB and MSI affect the sensitivity of immunotherapy and prognosis. The current study analyzed whether there is a correlation between SERCA3 expression and TMB and MSI in various cancers. From the analysis results it seems that SERCA3 expression was positively correlated with TMB in some cancers. A \( p \)-value for these cancers were UCEC \((0.0052)\), LGG \((0.0006)\), OV \((0.0035)\), COAD \((0.0360)\), ESCA \((0.0007)\), and GBMLGG \((<0.0001)\), while it was negatively associated with TMB in LIHC \((0.0002)\), TGCT \((0.0431)\), PAAD \((0.0016)\), PRAD \((<0.0001)\), LAML \((0.0131)\), GBM \((0.0089)\), THCA \((0.0004)\), STAD \((0.0018)\), THYM \((7.87e-11)\), KIRP \((0.0126)\), LUSC \((0.0403)\), and KIRC \((0.0137)\) (Figure 8(a)). Moreover, expression of SERCA3 was positively associated with MSI in some cancers. A \( p \)-value
for these cancers were COADREAD (0.0014), LUAD (<0.0001), COAD (<0.0001), and UCEC (0.0017), and was negatively correlated with MSI in TGCT (0.0224), STAD (0.005), LIHC (0.0202), DLBC (0.0136), KIPAN (2.16e-15), GBMLGG (0.0003), SARC (0.0231), HNSC (0.0161), and KIRP (0.0251) (Figure 8(b)).

4. Discussion

Calcium-dependent cell signal transduction was involved in a variety of life activities including proliferation, differentiation, secretion, and death [12]. Maintaining Ca$^{2+}$ homeostasis is crucial for protein storage and transport, signal transduction, and various cellular activities [11]. Abnormal changes in intracellular Ca$^{2+}$ levels have been reported to affect cancer progression [21, 22, 35, 36]. However, in cancer, the role of SERCA3, a protein that maintains Ca$^{2+}$ homeostasis in the cytoplasm and endoplasmic reticulum, remains unknown. In this study, the pan-cancer analysis revealed an association between SERCA3 expression and cancer prognosis, immunoregulatory genes, immune infiltration, and mutations.
Figure 3: Pan-Cancer Analysis of the Association between SERCA3 Expression and TNM classification and WHO cancer stages (a) The correlations between SERCA3 expression and TNM classification. (b) The correlations between SERCA3 expression and WHO cancer stages. *p ≤ 0.05 and **p < 0.01.
Figure 4: Prognostic analysis of SERCA3 expression. The forest map shows the influence of SERCA3 expression on overall survival (OS) evaluated by Cox proportional hazard regression model.

Figure 5: Continued.
We found that SERCA3 expression varied among different cancer types. SERCA3 was expressed at low levels in 13 types of cancers, including GBM, GBMLGG, LGG, COAD, COADREAD, KIRP, KIPAN, PRAD, LUSC, THCA, READ, BLCA, and KICH. Comparative analyses revealed high SERCA3 expression in two cancer types, including BRCA and CHOL. Moreover, SERCA3 expression is association with WHO cancer stages and TNM classification in a few types of cancer. For instance, the expression of SERCA3 is different for WHO cancer stages of GBM, GBMLGG, LGG, and BRCA. Furthermore, the expression of SERCA3 is related to metastasis stages of GBMLGG, LGG, and COADREAD. Cox regression analysis showed that SERCA3 is a protective factor against some cancers, including PAAD, SKCM, SARC, SKCM-M, HNSC, COADREAD, BLCA, COAD, CESC, KIRC, and OV. However, it acts also as a risk factor for GBMLGG, LGG, UVM, KIPAN, and TGCT. These results indicated that SERCA3 has a low level of expression in most cancers compared with its expression in normal tissues and plays a protective role in most cancer types.

Analysis of the results of the TCGA database revealed that the expression of SERCA3 was correlated with the chemokine receptors CCR4, which plays a significant role in immune regulation and is regarded as a potential therapeutic target in bronchial asthma. CCR4 is also highly expressed in adult T-cell leukemia/lymphoma (ATLL) and cutaneous T-cell lymphoma (CTCLs) [37]. Li et al. showed that overexpression of CCR4 mediates the chemotactic response of breast cancer cells to CCL17 and accelerates the growth and metastasis of breast cancer [38]. Our results found a correlation between the level of SERCA3 and immune-activating and immunosuppressive genes, including PDCD1 (PD-1), CTLA-4, TIGIT, and ICOS. By analyzing the correlation between SERCA3 expression and immune checkpoints we found that SERCA3 expression was related to immune checkpoints, including CTLA-4, PDCD1, and ICOS in most types of cancer. PDCD1 and CTLA-4 antibodies, which are immune checkpoint inhibitors, have been approved for the treatment of cancers including non-small cell lung cancer (NSCLC) and melanoma, and have improved the prognosis of patients with these cancers [39, 40]. These results proved that SERCA3 might partially affect immune checkpoints.

The tumor microenvironment (TME) is pivotal in regulating cancer progression and can predict treatment outcomes [41–43]. The composition of the TME is complex and includes vascular vessels, immune infiltrates, fibroblasts, and the extracellular matrix [44–46]. The immune cells, an important part of the TME, show an apparent impact on cancer development [46, 47]. Investigating the association of SERCA3 expression and levels of immune cell, we detected
that SERCA3 expression was positively associated with M1 macrophages and CD8+ T cells levels, whereas it showed a negative correlation with the levels of M0 and M2 macrophages. Cytotoxic CD8+ T cells are the main immune cells against pathogens and neoplastic cells. The cancer immunotherapy partially strengthens CD8+ T cell activity leading to the reduced escape of cancer cells from the immune system and then establishing durable and efficient anti-tumor immunity [48, 49]. SERCA3 may play a protective role in most cancers by increasing T cell infiltration.

Figure 6: Pan-cancer analysis of the SERCA3 expression in relation to immune checkpoints. The heatmap shows the correlation between SERCA3 expression and immune checkpoints. For each pair, the left top triangle is colored to represent the Spearman correlation coefficient; the right bottom one is colored to indicate the p-value. * p ≤ 0.05.

Figure 6: Pan-cancer analysis of the SERCA3 expression in relation to immune checkpoints. The heatmap shows the correlation between SERCA3 expression and immune checkpoints. For each pair, the left top triangle is colored to represent the Spearman correlation coefficient; the right bottom one is colored to indicate the p-value. * p ≤ 0.05.
Figure 7: Immune cell infiltration analysis. The heatmap shows the correlation between SERCA3 expression and immune cell infiltration levels. For each pair, the left top triangle is colored to represent the Spearman correlation coefficient; the right bottom one is colored to indicate the p-value. *p ≤ 0.05.

Figure 8: The Relationship between SERCA3 Expression and TMB and MSI (a) Map exhibits the correlations between SERCA3 expression and TMB. (b) Map exhibits the correlations between SERCA3 expression and MSI. Point size represents sample size, the larger the point, the larger the samples size; red color depth represents p value, the deeper the color, the smaller the p value.
Previous research reported that an increased M2/M1 macrophage ratio promotes cancer progression [50]. SERCA3 expression was positively correlation with M1 macrophage levels while negatively correlation with M2 macrophage levels, further providing a basis for the protective role of SERCA3 in most cancer types. These results suggest that SERCA3 may interfere with the prognosis of various cancers by regulating the expression of multiple immune cells.

Finally, we assessed the correlation among SERCA3 expression, TMB, and MSI. The more somatic mutations in tumors, the newer antigens that may form, and TMB can be used to evaluate the number of new tumor antigen loads [51]. MSI is an indicator of DNA mismatch repair (MMR) defects. TMB and MSI were used as biomarkers to predict the efficacy of immune checkpoint blockade (ICB) [52, 53]. By pan-cancer analysis we found that SERCA3 expression correlated with TMB and MSI, providing evidence for SERCA3 as a potential predictor of ICB therapy.

However, our study had some limitations. First, it was based on bioinformatics and different databases; methods of generating data may have impacted the results. Second, TCGA database lacks data on immunotherapy; hence, we cannot further analyze the indications for immunotherapy. Overall, our study systematically analyzed the association of SERCA3 expression with prognosis, immune modulator genes, immune checkpoints, immune cell infiltration, TMB, and MSI, which can provide information to further understand the role of SERCA3 in cancers and its relationship with the immune responses. It also provides a basis for considering SERCA3 as a potential cancer treatment target and biomarker. A potential challenge in the future will involve the development of new therapeutic methods related to the specific targeting of SERCA3 to limit the development and progression of cancer.

5. Conclusions

This research revealed that SERCA3 expression was significantly decreased in most types of cancer, cancer patients with reduced SERCA3 expression tend to have a poor prognosis. Moreover, we analyzed the correlation of SERCA3 expression with immune regulatory gene expression, immune checkpoints, immune cell infiltration, TMB, and MSI. We speculated that SERCA3 might affect cancer progression by regulating the TME, especially immune cells. These results provide new ideas for the function and role of SERCA3 in pan-cancer and provide a theoretical basis for considering SERCA3 as a potential cancer treatment target and biomarker.

Data Availability

The data used in this study can be found in the relevant literature, The Human Protein Atlas (HPA: https://www.proteinatlas.org), UCSC (https://xenabrowser.net), GDC (https://portal.gdc.cancer.gov), TCGA-SKCM, Solid Tissue Normal, Primary Blood Derived cancer-peripheral Blood and Primary Tumor.

Disclosure

Jiajia Li and Xionghui Li are co-first authors.

Conflicts of Interest

The authors declare no commercial or financial conflicts of interest related to this study.

Authors’ Contributions

Jiajia Li and Xionghui Li contributed equally to this manuscript. Conceptualization, Chenzi Zhang, Yanyun Xie, Yupeng Jiang and Jiajia Li; Data acquisition and analysis, Yupeng Jiang and Jiajia Li; Partial analysis method, Xionghui Li, Hong Huang and Lijian Tao.; writing original draft preparation, Jiajia Li.; Made important contribution in article revision, Xionghui Li.; writing review and editing, Chenzi Zhang, Yanyun Xie, Yupeng Jiang. All authors have read and agreed to the published version of the manuscript.

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Supplementary Materials

Supplement 1 Abbreviations of nouns. (Supplementary Materials)

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