Pan-Cancer dissection of ORAI1: prognostic implications and immune landscape correlation

Wan-Rong Li1,2, Jian Wang1,*, Xin Li1,2*

1Tianjin Cancer Hospital Airport Hospital, National Clinical Research Center for Cancer, Tianjin 300308, China. 2Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin’s Clinical Research Center for Cancer, Tianjin 300060, China.

*Corresponding to: Jian Wang, Xin Li. Tianjin Cancer Hospital Airport Hospital, No. 99, East 5 th Road, Tianjin Airport Economic Zone, Tianjin 300308, China.

E-mail: wangjians5862@163.com; xinli0809@gmail.com.

Abstract

Background: The ORAI1 gene, central to store-operated calcium entry (SOCE), is increasingly recognized for its pivotal role in cancer progression and patient prognosis across a broad spectrum of malignancies. Despite its critical involvement in calcium signaling pathways that are essential for cellular functions such as proliferation, migration, and apoptosis, the comprehensive impacts of ORAI1 within the tumor microenvironment (TME) and its modulation across various cancers have not been fully elucidated. Methods: We conducted a pan-cancer analysis leveraging data from The Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx) to assess ORAI1 expression. Differential expression analyses were performed, complemented by correlative studies with tumor mutation burden (TMB), microsatellite instability (MSI), immune infiltration, and key biological processes and pathways. Results: Our results demonstrate that ORAI1 is consistently upregulated in a range of cancer types, associated with aggressive tumor characteristics and poor patient outcomes. Significantly, ORAI1 upregulation correlates with increased tumor mutation burden (TMB) and microsatellite instability (MSI), markers of genomic instability that are predictive of response to immunotherapy, underscoring its potential utility in clinical stratification and treatment decision-making. ORAI1’s influence extends to the immune landscape, showing associations with immune cell infiltration and both immunosuppressive and immunostimulatory gene sets, thereby affecting the TME and possibly the efficacy of immunotherapeutic interventions. Conclusions: The multifaceted nature of ORAI1’s involvement in cancer pathophysiology positions it as a prospective biomarker and therapeutic target. Its expression dynamics and correlative significance with prognostic and immune regulatory elements underscore its potential in guiding therapeutic strategies and improving clinical outcomes. This study lays a foundation for future research, aiming to leverage ORAI1’s biological significance in cancer prognosis and therapy optimization.

Keywords: ORAI1; Pan-Cancer analysis; tumor microenvironment; immunotherapy; tumor mutation burden; microsatellite instability

Citation


Executive editor: Chen-Hui Dong.
Received: 26 January 2024; Accepted: 13 May 2024;
Available online: 16 May 2024.
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Background

The elucidation of cancer’s molecular underpinnings has undergone a paradigmatic shift with the advent of comprehensive pan-cancer analyses, aligning the expression profiles of pivotal genes with clinical outcomes [1–3]. Among these, ORAI1 emerges as a gene of consequence, implicated in the intricate ballet of calcium signaling and cellular homeostasis. Its role, transcending mere participation in store-operated calcium entry (SOCE), has implications that reverberate through the labyrinthine pathways of oncogenesis, metastasis, and the tumor microenvironment (TME) [4–6].

This study delves into the pan-cancer expression dynamics of ORAI1, a gene enconcened at the crossroads of calcium-mediated signaling and cancer pathophysiology [7, 8]. ORAI1’s aberrant expression patterns, underscored by its differential expression across a plethora of cancers, posit a critical inquiry into its dualistic nature in tumorigenesis. The propensity for heightened expression in the majority of cancers studied herein suggests a nefarious role in the orchestration of tumorigenic processes [9–11].

It is within this scientific tableau that we align ORAI1’s expression with key biological processes and pathways, leveraging the analytical robustness of the Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases. The gene’s correlation with processes such as lyase activity modulation and hormonal synthesis pathways underscores its multifaceted role in cellular function and cancer biology.

Furthermore, the prognostic landscape painted by ORAI1’s expression contours presents a variegated mosaic. Its association with overall survival, TMB, and MSI across diverse cancer types suggests a gene deeply entrenched in the prognostic architecture of malignancies. Such associations compel a reevaluation of ORAI1’s role, positing it as a potential harbinger of therapeutic outcomes, particularly in the realm of immunotherapeutic interventions.

The complex interplay between ORAI1 expression and immune cell infiltration provides critical insights into the tumor microenvironment (TME), suggesting that ORAI1 could significantly influence the immunological dynamics, potentially steering immune responses in favorable directions. The correlation with immune cell recruitment and activation signals a gene that may very well influence the immune landscape’s constitution, with implications for cancer prognosis and therapeutic efficacy.

As we stand on the precipice of a new era in cancer biology, the ORAI1 gene invites a reimagining of its role across the pan-cancer continuum. This study aims to unravel the multifaceted roles of ORAI1 in cancer, from its gene expression profiles to its clinical implications, thereby setting the stage for future research into its viability as a biomarker and therapeutic target.

Methods

Gene expression profiling and differential analysis

We extracted gene expression data for ORAI1 from several public databases, notably The Cancer Genome Atlas (TCGA) and the Genotype-Tissue Expression (GTEx) project, encompassing a broad spectrum of cancer types. We performed differential expression analysis to compare the levels of ORAI1 in tumor tissues against their corresponding normal tissues, utilizing stringent statistical criteria for robust comparisions. We established significance at a p-value threshold of less than 0.05 to ensure statistical rigor.

Matched tumor-normal pair analysis

For cancers with available matched normal samples, a comparative analysis was performed using violin plots to illustrate the expression dichotomy within individual cancer types. We employed statistical analyses, such as t-tests and ANOVA, to evaluate the variability in ORAI1 expression and its correlations with tumorigenic processes, ensuring comprehensive data interpretation.

Biological process and pathway enrichment analysis

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases were utilized to elucidate the biological processes and signaling pathways associated with ORAI1 dysregulation. Ridge plots and other graphical representations were created to visualize the gene’s involvement in cellular signaling and metabolic processes.

Correlation with TMB and MSI

The association between ORAI1 expression and tumor mutation burden (TMB) and microsatellite instability (MSI) was investigated across various cancer types. Statistical methods such as Spearman’s and Pearson’s correlation coefficients were calculated to reveal the strength and direction of these associations.

Prognostic analysis

The prognostic significance of ORAI1 expression was evaluated using hazard ratios (HRs) and 95% confidence intervals (CIs) across multiple cancers. Cox regression and Kaplan-Meier analyses were applied to assess the impact on overall survival (OS), progression-free interval (PFI), disease-free interval (DFI), and disease-specific survival (DSS).

Immune infiltration and chemokine signaling correlation analysis

Using algorithms like ESTIMATE and CIBERSORT, the study analyzed the correlation between ORAI1 expression and immune cell infiltration, as well as chemokine and chemokine receptor profiles across various cancer types. We constructed heatmaps to visualize the correlations, marking statistically significant results with asterisks to facilitate quick interpretation.

Statistical analysis

Statistical analyses were performed using R software and various packages tailored for bioinformatics research. Heatmaps, forest plots, and bubble plots were generated to visualize the data, and statistical significance was annotated accordingly. We applied a rigorous multiple testing correction using the False Discovery Rate (FDR) method to control for type I errors in our statistical analyses.

Data availability

Data supporting the findings of this study are available within the article and its supplementary materials or from the corresponding author upon reasonable request.

Results

Differential expression and correlative analysis of ORAI1 in Pan-Cancer

A comprehensive pan-cancer analysis was conducted to elucidate the expression dynamics of the ORAI1 gene, known for its role in store-operated calcium entry (SOCE) and implicated in numerous cellular functions including proliferation, migration, and survival. Figure 1A presents a boxplot representation, showcasing differential expression levels of ORAI1 in a multitude of cancer types juxtaposed against their normal tissue counterparts. The data demonstrate a significant upregulation of ORAI1 in the majority of cancer types, marked by higher median expression values in tumor samples compared to normal tissues, with few exceptions where a downregulation trend is observed.

Subsequent analysis of matched tumor-normal pairs, as delineated in Figure 1B, offers further insights into the expression dichotomy of ORAI1 within individual cancers. The violin plots emphasize the variance within each cancer type, capturing both the central tendency and dispersion of expression, thereby reinforcing the gene's dysregulated profile in the tumorigenic context.

Correlative significance of ORAI1 with biological processes and signaling pathways

Extending beyond expression analysis, Figure 1C and Figure 1D deploy Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases to map the biological and...
pathway-related ramifications of ORAI1 dysregulation. The gene’s involvement in ‘store-operated calcium entry’ and ‘positive regulation of lyase activity’ among other processes is visualized through a ridge plot in Figure 1C, suggesting a pivotal role in modulating intracellular signaling cascades and metabolic processes. Figure 1D further contextualizes ORAI1 within the framework of primary immunodeficiencies, platelet activation, cortisol synthesis and secretion, and the renin-angiotensin system, implicating the gene in an expansive array of physiological and pathological pathways. The ridge plot underscores the breadth of ORAI1’s impact, with potential implications for both endocrine and immune responses in the cancer milieu.

Figure 1 Pan-Cancer expression profile and biological significance of ORAI1. (A) Differential Expression of ORAI1 Across Cancer Types. Box plots representing the expression levels of ORAI1 across various cancer types compared to normal tissues. Data indicates a significant upregulation of ORAI1 in the majority of cancers, with notable exceptions where a downregulation is observed, delineating a pan-cancer perspective of ORAI1’s dysregulation. (B) Correlation of ORAI1 Expression in Tumor vs. Paired Normal Samples. Violin plots illustrating the comparative expression of ORAI1 between tumor samples and their matched normal counterparts across selected cancer types. Statistical analysis underscores the expression variability and the correlation between ORAI1 overexpression and tumorigenic processes. (C) Gene Ontology (GO) Analysis of ORAI1-Associated Biological Processes. A graphical representation of GO terms associated with ORAI1, emphasizing its involvement in crucial cellular processes such as store-operated calcium entry, positive regulation of lyase activity, and others, which are implicated in cancer cell signaling and homeostasis. (D) Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathway Analysis of ORAI1. A visualization of KEGG pathway enrichment for ORAI1, highlighting its influence on several pathways including platelet activation and various hormonal synthesis and secretion pathways. In all panels, statistical significance is denoted as follows: ns (not significant), \( P < 0.05 \), \( P < 0.01 \), \( P < 0.001 \), \( P < 0.0001 \).
Correlational analysis of ORAI1 expression with TMB and MSI across Pan-Cancer types

Figure 2A elucidates the correlation between ORAI1 expression and TMB across various cancer types. In a subset of cancers, including Uterine Corpus Endometrial Carcinoma (UCEC) and Adenocortical Carcinoma (ACC), a significant positive correlation was observed, denoted by asterisks, indicating a potential concordance between ORAI1 expression and TMB. Conversely, other malignancies, notably Lung Squamous Cell Carcinoma (LUSC) and Lung Adenocarcinoma (LUAD), demonstrated a negative correlation, suggesting an inverse relationship wherein increased ORAI1 expression may correlate with a lower TMB.

In Figure 2B, the relationship between ORAI1 and MSI across cancer types is represented. Akin to the TMB analysis, a positive correlation was noted in several cancers, with Cholangiocarcinoma (CHOL) and Diffuse Large B-Cell Lymphoma (DLBCL) being particularly noteworthy for their marked correlations. This suggests that ORAI1 may have a role in the MSI pathway, which is pivotal in the context of immune surveillance and therapy responsiveness. A minority of cancers displayed a negative correlation, indicating the heterogeneity of ORAI1’s role in cancer pathophysiology.

The observed correlative dynamics suggest a multifaceted role of ORAI1 in tumorigenesis and response to therapy. The positive correlations in certain cancer types may reflect an intrinsic link between ORAI1-mediated calcium signaling and genomic instability, potentially through influencing DNA repair mechanisms or affecting the tumor microenvironment. Conversely, the negative correlations observed may imply a context-dependent role of ORAI1, which might be influenced by the unique molecular and cellular landscapes of different tumor types.

Correlational analysis of ORAI1 gene expression with prognostic survival and cancer hallmarks across multiple tumor types

In elucidating the prognostic ramifications of ORAI1 gene expression across diverse cancer types, we observed a varied landscape of implications for overall survival (OS), as depicted in Figure 3A. The forest plot delineates the hazard ratios across multiple neoplasms, indicating that ORAI1 expression bears a statistically significant prognostic weight in specific contexts. For instance, in bladder urothelial carcinoma (BLCA) and kidney renal clear cell carcinoma (KIRC), elevated ORAI1 expression portends a riskier prognosis, manifesting in an augmented hazard ratio (HR > 1, P < 0.05). Conversely, in cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC) and head and neck squamous cell carcinoma (HNSC), the upregulation of ORAI1 appears to be a protective prognostic factor (HR < 1, P < 0.05).

A methodological bifurcation employing both Cox and log-rank approaches furnished us with a granular understanding of ORAI1’s prognostic impact on four survival outcomes, including OS, progression-free interval (PFI), disease-free interval (DFI), and disease-specific survival (DSS), as explicated in Figure 3B. Notably, in kidney renal papillary cell carcinoma (KIRP) and cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), ORAI1 expression levels are robustly associated with OS and PFI, offering a predictive nuance to the prognosis.

Delving into the nexus between ORAI1 gene expression and pan-cancer hallmark pathways, Figure 3C presents a vivid bubble plot that elucidates significant correlations. In the realms of breast invasive carcinoma (BRCA) and liver hepatocellular carcinoma (LIHC), high ORAI1 expression correlates with pathway pivotal for oncogenesis, such as WNT/β-catenin signaling pathway. The magnitude of these associations is underscored by the normalized enrichment score (NES) and the negative logarithm of the false discovery rate (FDR), presenting a compelling narrative of the gene’s role in tumorigenic processes.

Correlation of ORAI1 gene expression with immune infiltration in Pan-Cancer analysis

Figure 4A, utilizing the ESTIMATE algorithm, divulges a discernible correlation between ORAI1 expression and immune infiltration across various cancer types. Notably, a significant association is evident in cancers such as pancreatic adenocarcinoma (PAAD), liver hepatocellular carcinoma (LIHC), and sarcoma (SARC), where the immune scores are strikingly impacted by the expression of ORAI1. This correlation is underscored by a pattern where increased ORAI1 expression seems to parallel elevated immune scores, suggesting a potential facilitative role of ORAI1 in immune cell recruitment or activation within the tumor microenvironment (TME).

Delving deeper into the specifics of immune cell type association, Figure 4B, which employs the CIBERSORT algorithm, provides a granular view of the relationship between ORAI1 expression and the infiltration of distinct immune cell subsets across the cancer spectrum. Intriguingly, the expression of ORAI1 harbor’s a robust positive correlation with the infiltration of CD8+ T cells, particularly in cancers such as colon adenocarcinoma (COAD) and lung adenocarcinoma (LUAD). Meanwhile, a positive correlation is observed with regulatory T cells (Tregs) of multiple cancers, indicating a different microenvironment of multiple cancers fostered by ORAI1.
Figure 3 Multi-dimensional analysis of the ORAI1 gene's expression in relation to prognostic survival outcomes and hallmark cancer pathways across a spectrum of tumor types. (A) A forest plot delineating the hazard ratios (HRs) with 95% confidence intervals (CIs) assessing the impact of ORAI1 expression on overall survival (OS) across various cancers, with statistical significance denoted by p-values. (B) A heatmap utilizing two methodological approaches, Cox regression and log-rank tests, to evaluate the expression of ORAI1 against four survival endpoints: OS, progression-free interval (PFI), disease-free interval (DFI), and disease-specific survival (DSS). The colors represent the nature of the prognostic effect (risky or protective), and the methodological analysis applied. (C) A bubble plot exploring the correlation between high or low expression of the ORAI1 gene and activation or suppression of tumor hallmark pathways in different cancer types. Normalized Enrichment Score (NES) and False Discovery Rate (FDR) values are visualized, highlighting the strength and significance of these associations. The color intensity and size of the bubbles correspond to the NES and the significance level (-log10(FDR)), respectively.
Figure 4 Investigating the association of ORAI1 expression with immune infiltration across various cancer types. (A) Heatmap displaying the correlation between ORAI1 gene expression and immune infiltration scores in a pan-cancer context, employing the ESTIMATE algorithm. The immune infiltration scores include StromalScore, ImmuneScore, and ESTIMATEscore, across a range of cancer types denoted by their respective acronyms. The color intensity indicates the degree of correlation, with red representing a positive correlation and blue indicating a negative correlation. Statistically significant correlations are marked with asterisks, with the number of asterisks indicating the level of significance. (B) Heatmap showcasing the correlation of ORAI1 expression with the infiltration levels of specific immune cell types across various cancers, analyzed using the CIBERSORT algorithm. Each cell type's correlation is depicted, ranging from monocytes to T cells gamma delta, with red indicating a positive correlation and blue a negative correlation with ORAI1 expression. Significance levels are denoted by asterisks as per statistical convention.

Correlative analysis of ORAI1 expression with immunosuppressive and immunostimulatory gene sets across Pan-Cancer entities

In analyzing the intricate interplay between ORAI1 expression and immune gene signatures across a pan-cancer landscape, a meticulous investigation reveals pivotal associations that underpin the immunological undercurrents within the tumor microenvironment. Figure 5 delineates the correlation landscape between ORAI1 and a spectrum of immune regulatory genes, segregated into two distinct domains: immune suppressive (Figure 5A) and immune stimulatory (Figure 5B).

In the realm of immune suppression, the expression of ORAI1 exhibits a noteworthy positive correlation with pivotal checkpoint molecules such as PD-1 (PDCD1) and CTLA-4 across a range of malignancies, including but not restricted to, hepatocellular carcinoma (LJHC), lung adenocarcinoma (LUAD), and melanoma (SKCM). Notably, in glioblastoma multiforme (GBM), ORAI1’s relationship with these inhibitory axes implies a potential mechanistic nexus influencing tumor immune escape. Conversely, in the domain of immune activation, Figure 5B portrays ORAI1’s association with an array of stimulatory genes like CD40 and TNFSF13. This relationship appears to be robustly positive in cancers such as breast invasive carcinoma (BRCA) and kidney renal clear cell carcinoma (KIRC), suggesting that ORAI1 may partake in modulating the effector functions of immune cells.

Notably, in certain cancer types such as colorectal adenocarcinoma (COAD) and ovarian serous cystadenocarcinoma (OV), ORAI1’s correlation with immune stimulatory genes displays a diverse pattern, indicating a potential dual role in immune regulation. Such intricacies underscore the complexity of immune interactions and highlight the potential of ORAI1 as a biomarker for cancer immunotherapy efficacy.

Correlative analysis of ORAI1 expression with chemokine and chemokine receptor profiles across Pan-Cancer entities

In the quest to elucidate the intricate web of molecular interactions within the cancer microenvironment, a noteworthy endeavor was the analysis of the ORAI1 gene's expression and its correlation with a repertoire of chemokines and chemokine receptors across various cancer types. This cross-cancer investigation, delineated in Figure 6, casts light on the multifaceted roles of ORAI1 within the cancer milieu, potentially underpinning its utility as a prognostic marker or therapeutic target.

In Figure 6A, the heatmap presents a detailed correlation matrix, showcasing the expression patterns of ORAI1 alongside a pantheon of chemokines across a spectrum of cancers. Herein, the discernible patterns of co-expression become manifest, with some chemokines demonstrating robust positive correlations, whereas others exhibit an inverse relationship. Notably, in the context of cholangiocarcinoma (CHOL) and mesothelioma (MESO), the expression of ORAI1 appears to be positively correlated with a constellation of chemokines, including CXCL1 and CCL20, suggesting a nuanced dialogue between ORAI1 and these chemotactic cytokines that may influence the tumor's inflammatory and immune landscape.

Figure 6B, in a similar vein, portrays the association between ORAI1 expression and a cadre of chemokine receptors. Within this heatmap, it is observed that certain chemokine receptors, such as CXCR2 and CCR2, are inextricably linked to the expression of ORAI1 in malignancies like kidney renal papillary cell carcinoma (KIRC) and lymphoma (DLBC), suggesting that ORAI1 may partake in modulating the tumor microenvironment through its impact on chemokine receptor expression.
Figure 5 Interrogation of ORAI1 correlation with immune regulatory genes across diverse cancers. Panel A exhibits a heatmap delineating the correlation coefficients between ORAI1 and an array of immunosuppressive genes across various cancer types. The intensity of the red hue signifies a positive correlation, while the blue hue indicates a negative correlation, with asterisks denoting statistical significance (\*P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001). Panel B extends this analysis to immunostimulatory genes, providing a comparative landscape of ORAI1’s association with immune activation markers. The depicted correlations underscore the multifaceted role of ORAI1 in modulating the immune landscape within the tumor microenvironment, suggesting its potential utility as a biomarker for immune response and therapeutic targeting.
Figure 6 Interplay between ORAI1 expression and chemokine signaling in Pan-Cancer analysis. (A) Heatmap representing the correlation coefficients between ORAI1 gene expression and various chemokine genes across multiple cancer types. Each cell in the heatmap denotes the Pearson correlation coefficient, with the color intensity reflecting the strength and direction of the correlation (red for positive, blue for negative). Significant correlations are marked by asterisks, with the number of asterisks indicating the level of statistical significance (\( \ast P < 0.05 \), \( \ast\ast P < 0.01 \), \( \ast\ast\ast P < 0.001 \), \( \ast\ast\ast\ast P < 0.0001 \)). (B) Heatmap illustrating the correlation of ORAI1 expression with the expression of chemokine receptors across the same cancer cohort. The correlation coefficients are visualized as in (A), providing insights into the potential influence of ORAI1 on chemokine receptor-mediated signaling pathways within the tumor microenvironment.

Discussion

The present study undertakes a meticulous pan-cancer analysis to comprehend the multifarious roles of ORAI1, a gene instrumental in store-operated calcium entry (SOCE), across a diverse spectrum of malignancies. The results elucidate a statistically significant upregulation of ORAI1 in a majority of cancer types, underscoring its putative role in oncogenesis and potential as a therapeutic target. Notably, in certain cancer contexts, such as uterine corpus endometrial carcinoma and adrenocortical carcinoma, ORAI1 expression correlates positively with tumor mutation burden (TMB), while in others, like lung squamous cell carcinoma and lung adenocarcinoma, an inverse correlation emerges, hinting at the gene's complex involvement in cancer pathophysiology.
The intricacies of ORAI1’s interaction with biological processes and signaling pathways, as revealed through Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases, affirm its participation in cellular mechanisms pivotal to cancer progression. The gene's association with pathways such as WNT/ß-catenin and PI3K-AKT-mTOR, as suggested by the normalized enrichment scores (NES) and false discovery rates (FDR), supports its potential role in tumorigenic processes [12–14].

Furthermore, the study's findings on ORAI1's correlation with immune infiltration highlight its possible influence on the tumor microenvironment (TME). The observed positive association with regulatory T cells (Tregs) in certain cancers, contrasted with a negative correlation with CD8+ T cells, implies a gene-dependent modulation of the immune milieu, which could have implications for cancer immunotherapy efficacy. In the nuanced orchestration of the tumor microenvironment (TME), the interplay between various cells and signaling molecules defines the therapeutic landscape, particularly the response to immunotherapy. The apparent contradiction in the analysis results for certain cancers, such as adrenocortical carcinoma (ACC), can be ascribed to the intricate dynamics of the TME. Although the StromalScore, ImmuneScore, and ESTIMATEScore in ACC may not present a clear correlation, suggesting a limited direct impact on immunotherapy response, the positive association of ORAI1 with chemokines such as CXCL1 and CCL20 hints at a more covert interplay. This subtle dialogue suggests that while the broader immune scores may not indicate a significant response to immunotherapy, ORAI1 may still modulate the TME through chemotactic cytokines. These cytokines could orchestrate a localized immune response, potentially creating niches within the TME that could be responsive to therapy or affect tumor growth and progression.

Moreover, the discrepancy observed between macrophage immune checkpoint CD86 expression and macrophage infiltration across different cancers underscores the complexity of immune regulation within the TME. CD86 may not uniformly predict macrophage infiltration due to the myriad of factors influencing macrophage behavior, including other checkpoint molecules, the presence of other immune cells, and the influence of the local metabolic environment [15, 16]. A deeper dive into the specific conditions that lead to these contradictions is essential. Such an analysis could reveal the underlying reasons for the lack of alignment between immunocytology analysis results and other measures of immune activity. Dissecting these interactions could elucidate new targets for therapy or new methods to enhance existing treatments, particularly in cancers where the immune component of the TME is not straightforwardly characterized by traditional scoring methods.

Delving deeper into the cancer-specific pathways regulated by ORAI1 and their implications for immunotherapy and diagnostic prognosis, our study uncovers a nuanced regulatory landscape. In certain cancer types such as kidney clear cell carcinoma and kidney papillary cell carcinoma, ORAI1 expression is correlated with pathways involving cell proliferation and survival, indicating its potential as a prognostic biomarker. Specifically, in these cancers, elevated ORAI1 levels could signify a poor prognosis, reflecting its role in enhancing tumor growth and resistance to apoptosis.

Further analysis revealed that ORAI1 is involved in numerous signaling pathways critical for cancer progression, including the PI3K/AKT, WNT/ß-catenin, and MAPK pathways, which are pivotal for cell proliferation, migration, and survival. The modulation of these pathways by ORAI1 not only highlights its role in tumor growth and metastasis but also its potential as a target for multi-modal cancer therapy. For instance, the interaction of ORAI1 with the PI3K/AKT pathway suggests that inhibitors of ORAI1 could synergistically enhance the efficacy of PI3K or AKT inhibitors currently in clinical use. Moreover, the association of ORAI1 expression with poor prognosis in several cancers underscores its potential as a prognostic marker, where high ORAI1 expression could identify patients at higher risk of aggressive disease, who might benefit from more intensive treatment regimens.

In the context of immunotherapy, ORAI1’s modulation of immune cell infiltration emerges as a pivotal mechanism. For instance, in adrenocortical cancer and uterine carcinosarcoma, a high expression of ORAI1 correlates with increased tumor mutation burden (TMB) and microsatellite instability (MSI), which are predictive markers for the efficacy of immune checkpoint inhibitors. This implies that patients with higher ORAI1 expression in these cancers may exhibit a better response to immunotherapies targeting PD-1 or CTLA-4, making ORAI1 a potential biomarker for immunotherapy suitability.

Moreover, the relationship between ORAI1 expression and the immune microenvironment varies across cancers. In thyroid cancer and acute myeloid leukemia, ORAI1 may contribute to an immunosuppressive milieu, dampening the effectiveness of immune-based treatments. This contrast highlights the complexity of ORAI1’s role in cancer immunology and underscores the necessity of cancer-specific studies to understand its implications fully.

The clinical implications of our findings extend beyond simple prognostication, suggesting potential roles for ORAI1 in therapy customization. Given its involvement in key genetic pathways and the immune environment, ORAI1 could be targeted either to suppress its expression in cases where it promotes tumor growth and immune evasion, or alternatively, its activity could be enhanced in scenarios where it supports immune activation against the tumor. Future clinical trials should explore the therapeutic manipulation of ORAI1, either through direct inhibitors/activators or through its regulatory mechanisms, to fully harness its potential in oncology. Additionally, the integration of ORAI1 expression profiling in routine diagnostic panels could significantly improve the precision of cancer therapy, particularly in the era of personalized medicine.

The study's comprehensive analysis also extends to the gene's interplay with chemokine signaling. The correlation matrix, highlighting the co-expression patterns of ORAI1 with a range of chemokines and chemokine receptors, signifies its probable part in sculpting the inflammatory and immune landscape of the tumor. This nexus might prove significant for devising prognostic markers and tailoring therapeutic strategies.

In conclusion, ORAI1 emerges as a gene of profound clinical interest within oncology, implicated in extensive regulatory networks that influence tumor behavior and patient outcomes. The dualistic nature of its function suggests sophisticated therapeutic strategies that could inhibit its activity in contexts where it promotes cancer progression, or alternatively, enhance its function to boost anti-tumor immunity. Future research should focus on unraveling these complex interactions through advanced genomic and proteomic studies, which will pave the way for innovative treatments that are finely adjusted to the molecular profiles of individual tumors.

References


