Original Paper

A Comprehensive Pan-Cancer Analysis of the Mitochondrial Uncoupling Protein UCP2, with a Focus on Sex and Gender-Related Aspects

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Key Words
UCP2 • Pan-cancer • Gender-related cancers • Expression • Prognosis.

Abstract:
Background/Aims: Mitochondrial uncoupling protein 2 (UCP2) plays a crucial role in regulating oxidative stress and cellular metabolism, positioning it as an important subject in oncological research. The involvement of UCP2 in cancer is complex and context-dependent, suggesting it as a potential therapeutic target. In this study, we aimed to perform a comprehensive pan-cancer analysis of UCP2, with a particular focus on gender-related malignancies such as breast (BRCA), prostate (PRAD), ovarian (OV), and testicular tumors (TGCT). ***Materials:*** We analyzed *UCP2* expression in The Cancer Genome Atlas (TCGA), examining correlations with prognosis, tumor mutational burden (TMB), microsatellite instability (MSI), immune cell infiltration, immune checkpoint genes, genes involved in steroidogenesis, sex hormone receptor genes, and drug sensitivity. ***Results:*** Significant variability in UCP2 expression was observed across cancer types. *UCP2* levels were elevated in BRCA and OV but reduced in PRAD and TGCT. High *UCP2* expression was associated with a better prognosis in OV and poorer overall survival in PRAD. Furthermore, *UCP2* correlated with TMB and MSI in OV, TGCT, and BRCA. *UCP2* expression was also linked to immune cell infiltration, immune checkpoint genes, steroidogenic genes, and sex hormone receptor genes, with variable effects depending on cancer type and gender. Additionally, *UCP2* also demonstrated sensitivity to specific anticancer drugs. ***Conclusions:*** Our findings highlight the interplay between UCP2, immune and hormonal pathways, and drug response and reveal potential opportunities for new therapeutic combinations, especially in gender-related cancers.

V. Checchetto and T. Varanita contributed equally to this work.

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Introduction

Cancer development involves unique metabolic changes, now considered hallmarks of carcinogenesis [1]. Otto Warburg was the first to observe that cancer cells, even in the presence of oxygen rely mainly on glycolysis, rather than oxidative phosphorylation (OXPHOS), for energy production. This metabolic rewiring, known as the "Warburg effect," was initially attributed to reduced mitochondrial activity in cancer cells. Additional studies have demonstrated that many cancer cells have intact mitochondria, crucial for their metabolism and various cellular processes, including proliferation, survival in a challenging microenvironment, and metastasis [2, 3]. Mitochondria are essential for providing eukaryotic cells with energy in the form of ATP [4]. The metabolic breakdown of nutrients generates electrons, which are transferred through the electron transport chain (ETC) located in the inner mitochondrial membrane (IMM), generating a proton gradient across the IMM and establishing the mitochondrial potential essential for ATP synthase to produce ATP from ADP and inorganic phosphate [5]. In addition to ATP production, the ETC also generates reactive oxygen species (ROS), which play a role in homeostatic signaling but can also cause oxidative stress in disease conditions [6]. The ETC is vulnerable to ROS production under conditions of high electron flow and elevated mitochondrial membrane potential. Thus, uncoupling oxidative phosphorylation (OXPHOS) can reduce respiration rate and decrease mitochondrial ROS production. Physiologically, mitochondrial OXPHOS is not fully coupled to ATP production. Protons can leak back into the mitochondrial matrix from the IMS, bypassing ATP synthase and generating heat instead of ATP. These events can be regulated by uncoupling proteins (UCPs), a family of proton transporters located in the IMM [7],[8]. Among the UCPs, UCP2 is the most ubiquitously expressed, found in multiple cell types. The role of UCP2 in ATP production has been extensively investigated in numerous studies, particularly in pancreatic β-cells, identifying UCP2 as a negative regulator of ATP levels. By promoting proton leakage across the IMM, UCP2 lowers the mitochondrial membrane potential and reduces ATP synthesis [9, 10, 11, 12].

UCP2 has been identified as a crucial regulator of ROS in various cell types. It functions by mildly uncoupling OXPHOS, which reduces the mitochondrial membrane potential and ROS production. This activity provides an antioxidant effect, which helps to protect cells from oxidative damage. However, the role of UCP2 in uncoupling OXPHOS and its impact on ROS regulation remains under debate [13, 14, 15, 16, 17, 18, 19]. In addition, UCP2 emerged as a crucial regulator of cellular metabolism [20]. Therefore, several research studies acknowledged its involvement in various physiological and pathological conditions [21, 22]. In physiological conditions, UCP2 exerts tissue-specific roles essential to protecting cells from oxidative stress, maintaining metabolic homeostasis, and regulating immune responses. Its dysregulation is linked to a range of pathological conditions, including metabolic disorders and cancer. While UCP2 has been extensively studied in cancer in recent years, its exact role in carcinogenesis remains ambiguous. UCP2 is often highly expressed in cancer. Several cancer types have established a correlation between elevated UCP2 expression and tumor progression, highlighting its potential as a therapeutic target to treat UCP2 overexpressing cancers [23, 24]. Conversely, other studies have shown that UCP2 overexpression reduces tumorigenicity, alters mitochondrial signaling, and enhances chemotherapeutic-induced apoptosis by acting as a metabolic tumor suppressor [25, 26]. Interestingly, as a metabolic sensor, UCP2 regulates mitochondrial substrate oxidation by modulating the exchange of critical metabolites, influencing cellular energy balance and metabolic pathways in response to varying nutrient availability [27]. Therefore, UCP2 is implicated in the metabolic adaptations of cancer cells beyond its traditional uncoupling [28, 29, 30].

The tumor microenvironment (TME) immune composition and the immune profile of patients are increasingly recognized as critical determinants of cancer progression, therapeutic response, and prognosis [31, 32, 33, 34]. UCP2 intrinsically modulates tumor cell proliferation and chemoresistance, influencing their ability to evade immunosurveillance [35]. Furthermore, UCP2 is expressed in immune cells, including macrophages [36]. As major

immune infiltrates in solid tumors, macrophages adapt to the hypoxic tumor environment by reprogramming their metabolism in an activation state that promotes tumor growth [37]. In the TME, macrophages adopt distinct activation states and metabolic profiles. Pro-inflammatory (M1) macrophages, characterized by glycolytic metabolism, exhibit anti-tumorigenic properties, while anti-inflammatory (M2) macrophages, which rely on OXPHOS, display protumor activities [38]. UCP2 is involved in the polarization and metabolism of macrophages. During M1 polarization, UCP2 is downregulated, while its overexpression decreases macrophage ROS production, promotes metabolic rewiring towards OXPHOS, and re-polarization from M1 to M2 phenotype [39]. Therefore, UCP2 is an exciting target for understanding the molecular mechanisms behind metabolic reprogramming and macrophage activation in cancer. Further studies are necessary to clarify the role of UCP2 in macrophages in cancer development and progression. More recently, UCP2 has been suggested to play a role in steroidogenesis *in vitro* and *in vivo*, specifically affecting sex hormone production. More recently, UCP2 has been suggested to play a role in steroidogenesis *in vitro* and *in vivo*, specifically affecting sex hormone production [40]. Additionally, there is evidence to indicate that sex hormones could influence the expression of UCP2 [41, 42], which has led to speculations that UCP2 might be involved in regulating gender-specific variations in disease responses, including cancer.

In this study, we conducted a comprehensive pan-cancer analysis of UCP2 using data from The Cancer Genome Atlas (TCGA). Our investigation focused on UCP2 expression patterns, prognostic significance, genetic alterations, tumor mutational burden (TMB), microsatellite instability (MSI), immune infiltration, and the involvement of genes related to immunotherapy, steroidogenesis, and sex hormone receptors in the TCGA dataset. Special emphasis was placed on gender-related cancers, specifically breast (BRCA), prostate (PRAD), ovarian (OV), and testicular (TGCT) cancers (Fig. 1).

Materials and Methods

Data processing
The TCGAbiolinks R package (v2.32.0) along with BiocManager (v1.30.23) were employed to download TPM matrix, clinical information, TMB, and methylation matrices for the 33 types of cancers available in TCGA (https://portal.gdc.cancer.gov/). This was achieved using the functions GDCquery, GDCdownload, and GDCprepare. The expression matrix was generated using the formula log2(TPM+1) and prepared using the TCGAplot R package (v7.0.1)[43]. No data quality checks were performed. The ggpubr R package (v0.6.0) was used to compare and plot UCP2 expression across different tissues.

AUC analysis
TCGA tumors with enough normal samples were selected for Area Under the Curve (AUC) analysis based on *UCP2* expression. The pROC R package (v1.18.5) was used to assess the diagnostic potential of *UCP2* in distinguishing tumor
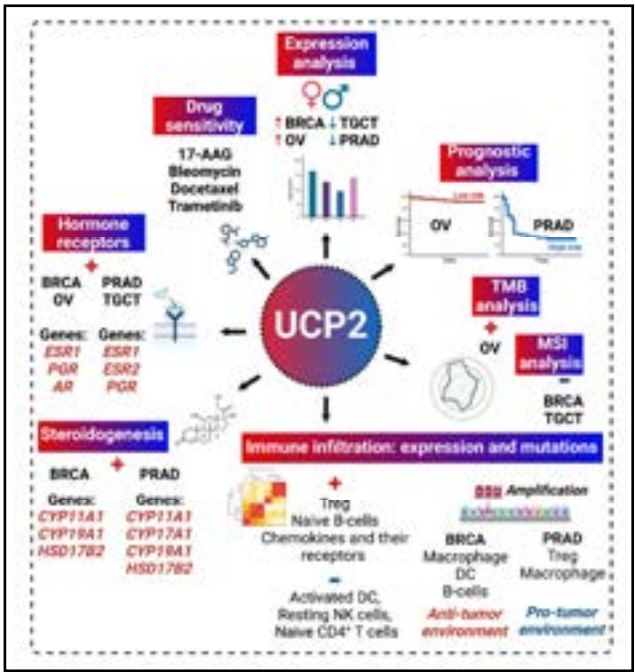
Fig. 1. Graphical abstract. The graphical abstract illustrates the methodology and key findings, including UCP2 expression, prognosis, correlations with TMB, MSI, immune infiltration, steroidogenic genes, sex hormone receptor genes, and drug sensitivity in BRCA, PRAD, OV, and TGCT cancer types.

samples from normal samples. The ROC curve was plotted, and the AUC and the 95% confidence interval (CI) were presented.

Prognosis potential analysis of UCP2
Overall Survival (OS) was evaluated to assess the predictive potential of UCP2. The survminer (v0.4.9) and survival (v3.6-4) R packages were used to perform the log-rank test and to generate Kaplan-Meier (KM) plots for data grouped by *UCP2* expression. The survival and forestplot (v3.1.3) R packages were employed to conduct Cox proportional hazards analysis to determine the relationship between *UCP2* expression and survival across 33 types of cancers in TCGA.

Correlation of UCP2 expression with mutational tumor heterogeneity
The correlation between *UCP2* expression and Tumor Mutational Burden (TMB) or Microsatellite Instability (MSI) was assessed using Pearson correlation analysis. The radar plot illustrating these correlations was generated using the fmsb R package (v0.7.6).

Relationship between UCP2 expression and immunity
A list of immune-related genes was downloaded from TISIDB (http://cis.hku.hk/TISIDB/index.php) [44]. The correlation between *UCP2* expression and immune-related genes and immune infiltration was examined using Pearson correlation analysis. The results were visualized using the ggplot2 R package (v3.5.1). The estimate R package (v1.0.13) was used to compute each specimen's immune, stromal, and estimate scores for each specimen. Pearson correlation analysis assessed the relationship between *UCP2* expression and these scores. The correlations were plotted using the ggplot2 (v3.5.1) and ComplexHeatmap (v2.20.0) R packages.

Biological significance of UCP2 in tumors
Cancer specimens were divided into *UCP2* high and low-expression subgroups. Differentially regulated genes between these subgroups were identified using the limma R package (v3.60.4). All genes were ranked by fold change (high-risk vs low-risk group) and used as input for GSEA-GO and GSEA-KEGG analyses. These analyses were performed using the org.Hs.eg.db (v3.19.1) and clusterProfiler (v4.12.1) R packages, with data from the KEGG database (https://www.kegg.jp/kegg/). The top five terms were visualized using the enrichplot R package (v1.24.2).

Drug sensitivity analysis
Gene Set Cancer Analysis (GSCA, http://bioinfo.life.hust.edu.cn/GSCA/#/, accessed on 29 July 2024) is an integrated genomic, pharmacogenomic, and immunogenomic gene set cancer analysis platform. This platform was utilized for drug sensitivity analysis related to *UCP2* expression.

RNA expression in single-cell clusters
UMAP plots were generated to visualize the human expression of *UCP2* in single cells across BC, OV, PRAD, and TGCT cancers.

Results

Expression and prognostic analysis of UCP2 in human cancers
The expression of *UCP2* was evaluated across various tumor types using data from the TCGA database (Table S1). When comparing the expression of *UCP2* between tumor and normal tissues, we found a significant increase in 9 types of tumors, including bladder cancer (BLCA), breast cancer (BRCA), cholangiocarcinoma (CHOL), esophageal cancer (ESCA), glioblastoma multiforme (GBM), lung adenocarcinoma (LUAD), stomach adenocarcinoma (STAD), thyroid carcinoma (THCA), and uterine corpus endometrial carcinoma (UCEC) (Fig. 2A, Table S2). In contrast, reduced *UCP2* expression was observed in kidney chromophobe (KICH), lung squamous cell carcinoma (LUSC), pancreatic adenocarcinoma (PAAD), and

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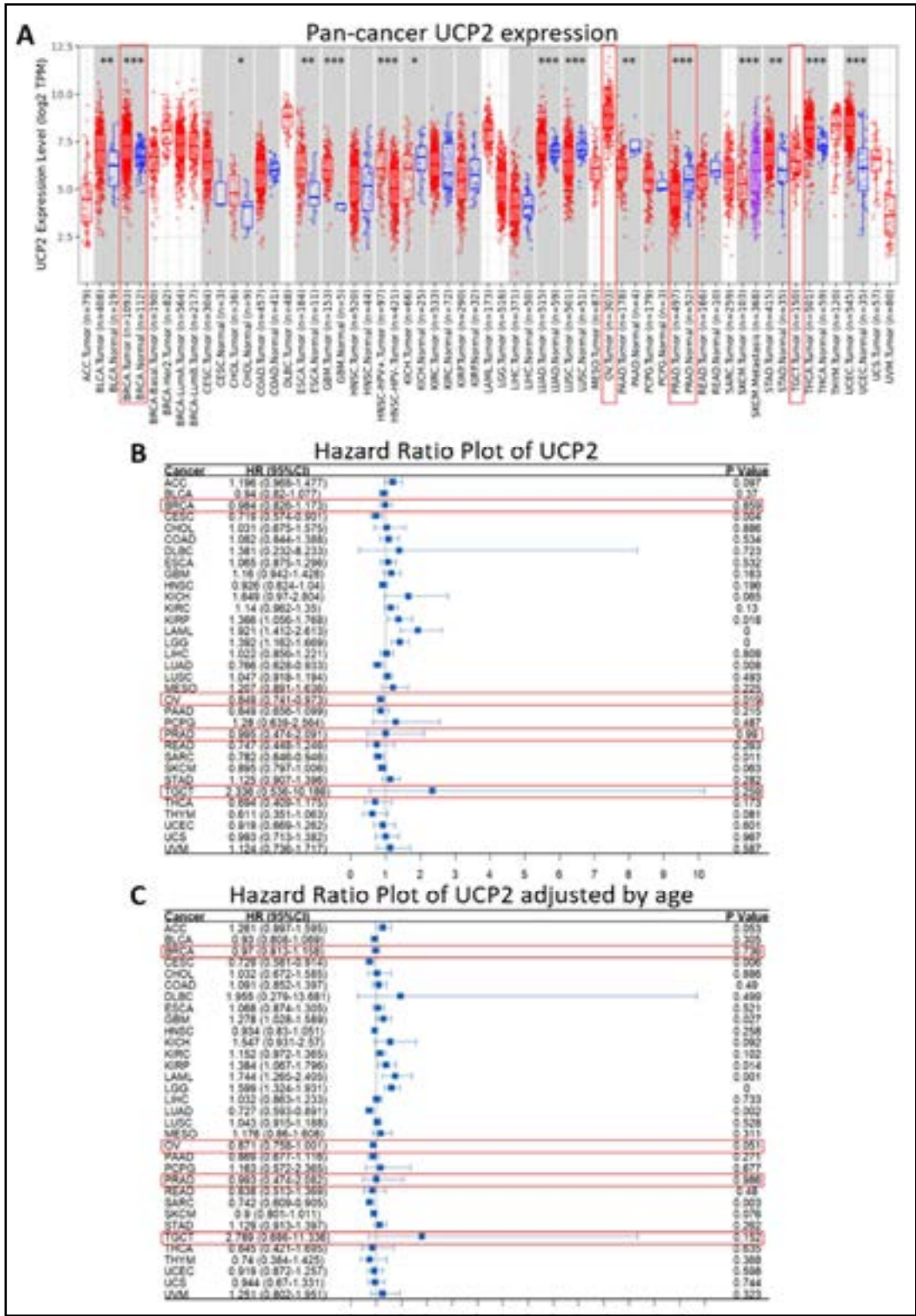
Fig. 2. Expression patterns of UCP2 across various cancer types. (A) TIMER2.0 analysis illustrating UCP2 expression levels in TCGA cancers compared to normal tissues, with significance denoted as ***p<0.001; **p<0.01; *p<0.05. Pan-cancer risk analysis. Pan-cancer Cox proportional hazards model analysis of UCP2 across 33 types of tumors in TCGA. The Wilcoxon test was used to compare UCP2 expression between normal and tumor groups, with significance indicated as ****p<0.0001, ***p<0.001, **p<0.01, *p<0.05, and ns denoting no significant difference. The function provides the ability to perform pan-cancer Cox regression analysis without (B) or with age adjustment (C), visualized by a forest plot.

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prostate adenocarcinoma (PRAD) (Fig. 2A, Table S2). We were unable to detect significant differences in *UCP2* expression in BRCA-Basal, BRCA-Her2, BRCA-LumA, BRCA-LumB, diffuse large B-cell lymphoma (DLBC), acute myeloid leukemia (LAML), low-grade glioma (LGC), mesothelioma (MESO), ovarian cancer (OV), sarcoma (SARC), testicular germ cell tumors (TGCT), uterine carcinosarcoma (UCS), and uveal melanoma (UVM) due to the lack of normal tissue data for comparison (Fig. 2A, Table S2). We then investigated the levels of *UCP2* expression in normal tissues and cancer cell lines using data from the Human Protein Atlas (HPA). In normal tissues, higher expression of *UCP2* was found in lymphoid organs, followed by the female reproductive system. In contrast, low expression was observed in the male reproductive system and most brain regions (Fig. S1A). Additionally, higher *UCP2* expression was identified in macrophages of adipose and liver tissues (Fig. S1B). Among cancer cell lines, the highest *UCP2* expression was found in lymphoma cells, followed by leukemia, adrenocortical, and breast cancer cell lines (Fig. S1C).

Next, we examined the predictive significance of *UCP2* expression on cancer patient survival using the Pan-cancer Cox proportional hazards model (HR) (Fig. 2B, C; Table S3). The overall survival (OS) results revealed that *UCP2* expression is a risk factor in kidney renal papillary cell carcinoma (KIRP) (HR = 1.336, p = 0.018), acute myeloid leukemia (LAML) (HR = 1.921, p = 0.0002), and brain lower grade glioma (LGG) (HR = 1.392, p = 0.0002). Conversely, it was associated with improved survival outcomes in cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC) (HR = 0.719, p = 0.004), lung adenocarcinoma (LUAD) (HR = 0.766, p = 0.008), ovarian serous cystadenocarcinoma (OV) (HR = 0.849, p = 0.019), and sarcoma (SARC) (HR = 0.782, p = 0.011) (Fig. 2B, Table S3). The age-adjusted hazard ratio analysis revealed that *UCP2* expression is a risk factor in glioblastoma multiforme (GBM) (HR = 1.278, p = 0.027), kidney renal papillary cell carcinoma (KIRP) (HR = 1.384, p = 0.014), acute myeloid leukemia (LAML) (HR = 1.744, p = 0.001), and brain lower grade glioma (LGG) (HR = 1.599, p = 0.0002) (Fig. 2C, Table S4). Additionally, it suggested that *UCP2* is a protective factor in cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC) (HR = 0.729, p = 0.006), ovarian serous cystadenocarcinoma (OV) (HR = 0.871, p = 0.051), lung adenocarcinoma (LUAD) (HR = 0.727, p = 0.002), and sarcoma (SARC) (HR = 0.742, p = 0.003) (Fig. 2C, Table S4). These results indicate that UCP2 levels vary among different cancer types, showing elevated expression in certain tumors, including breast cancer, and decreased levels in others, such as prostate cancer. It represents a risk factor in some tumors with downregulated *UCP2* levels while correlating with beneficial outcomes in others with increased *UCP2* levels, such as ovarian cancer.

Genomic mutations, TMB, and MSI analysis of UCP2 in pan-cancer

We used the cBioPortal Database to examine *UCP2* genetic variations in the TCGA pan-cancer cohort. *UCP2* genetic alterations, including amplifications, mutations, and deep deletions, were observed in many cancers. *UCP2* amplifications were most common in ovarian (OV) and breast (BRCA) cancers. Meanwhile, mutations were most prevalent in kidney chromophobe (KICH), and deep deletions were characteristic of testicular germ cell tumors (TGCT) (Fig. 3A).

Tumor mutational burden (TMB) and microsatellite instability (MSI) are molecular markers associated with tumor immunogenicity and can be used as potential biomarkers to predict responses to immunotherapy [45, 46]. We conducted a Pearson correlation analysis to explore the connection between *UCP2* expression and these markers. Our research uncovered a significant positive correlation between *UCP2* expression and TMB in ovarian cancer (OV), and a negative correlation was found in kidney renal papillary cell carcinoma (KIRP) (Fig. 3B). *UCP2* was negatively linked with MSI in testicular germ cell tumors (TGCT), breast invasive carcinoma (BRCA), KIRP, lung squamous cell carcinoma (LUSC), and stomach adenocarcinoma (STAD), while it showed a positive correlation exclusively in lung adenocarcinoma (LUAD) (Fig. 3C). In conclusion, considering gender dependent cancers, these results indicate that *UCP2* amplifications are frequent in OV while deletions occur in TGCT, and *UCP2* may affect antitumor immunity through its association with TMB and MSI
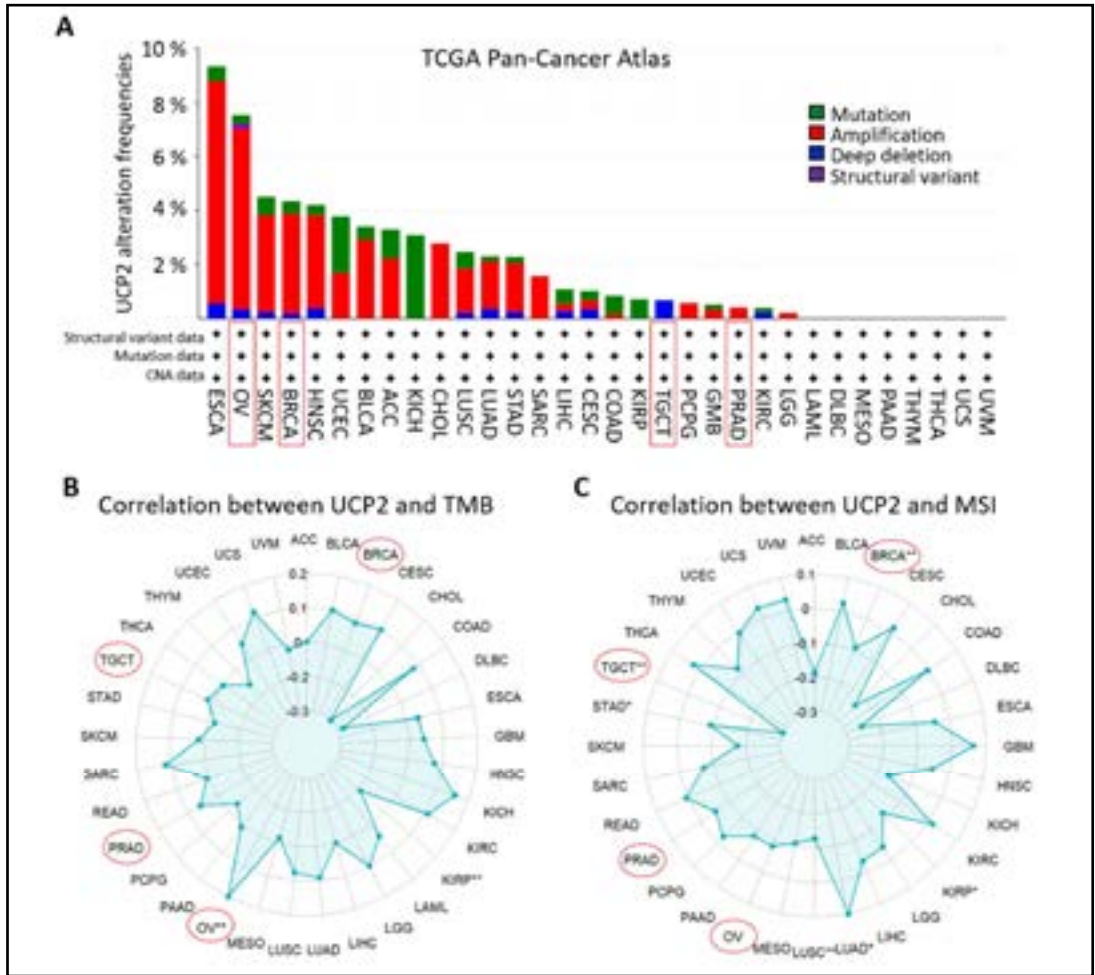
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Fig. 3. Mutation analysis of UCP2, correlation with TMB and MSI in pan-cancer. (A) Analysis using cBioPortal revealed the mutation types, frequencies, and sites of UCP2 across various cancer types. (B) Pan-cancer correlation analysis of UCP2 with Tumor Mutational Burden (TMB). (C) Pearson correlation analysis was used to calculate the correlation between UCP2 expression and MSI, with significance indicated as **$p<0.01$ and *$p<0.05$. They were generated using the TCGAplot R package (v7.0.1) (https://github.com/tjhwangxiong/TCGAplot).

in these cancers.

Correlation analysis of UCP2 expression with immune cell infiltration and checkpoint genes in pan-cancer

Considering the crucial role of the tumor immune microenvironment, its impact on clinical outcomes [47], and the established involvement of UCP2 in the immune system [48], we investigated the correlation between *UCP2* expression and immune cell infiltration in human cancers. Significant positive correlations between *UCP2* and stromal, immune, and estimate scores were found in almost all cancers. In contrast, only a few types of tumors, including ovarian cancer, showed no correlations with immune characteristics (Fig. 4A). Furthermore, in most tumor samples from the 33 tumor types, *UCP2* expression was positively correlated with regulatory T cells (Tregs) and naive B cells, while showing negative associations with activated dendritic cells (DC), resting NK cells, and naive CD4+ T cells (Fig. 4B). Targeting tumor immune infiltrates alone or in combination with immunotherapy can improve patient outcomes [38]. Therefore, we evaluated the correlation between *UCP2* gene expression and immune checkpoint-associated genes in cancers from the TCGA. *UCP2*

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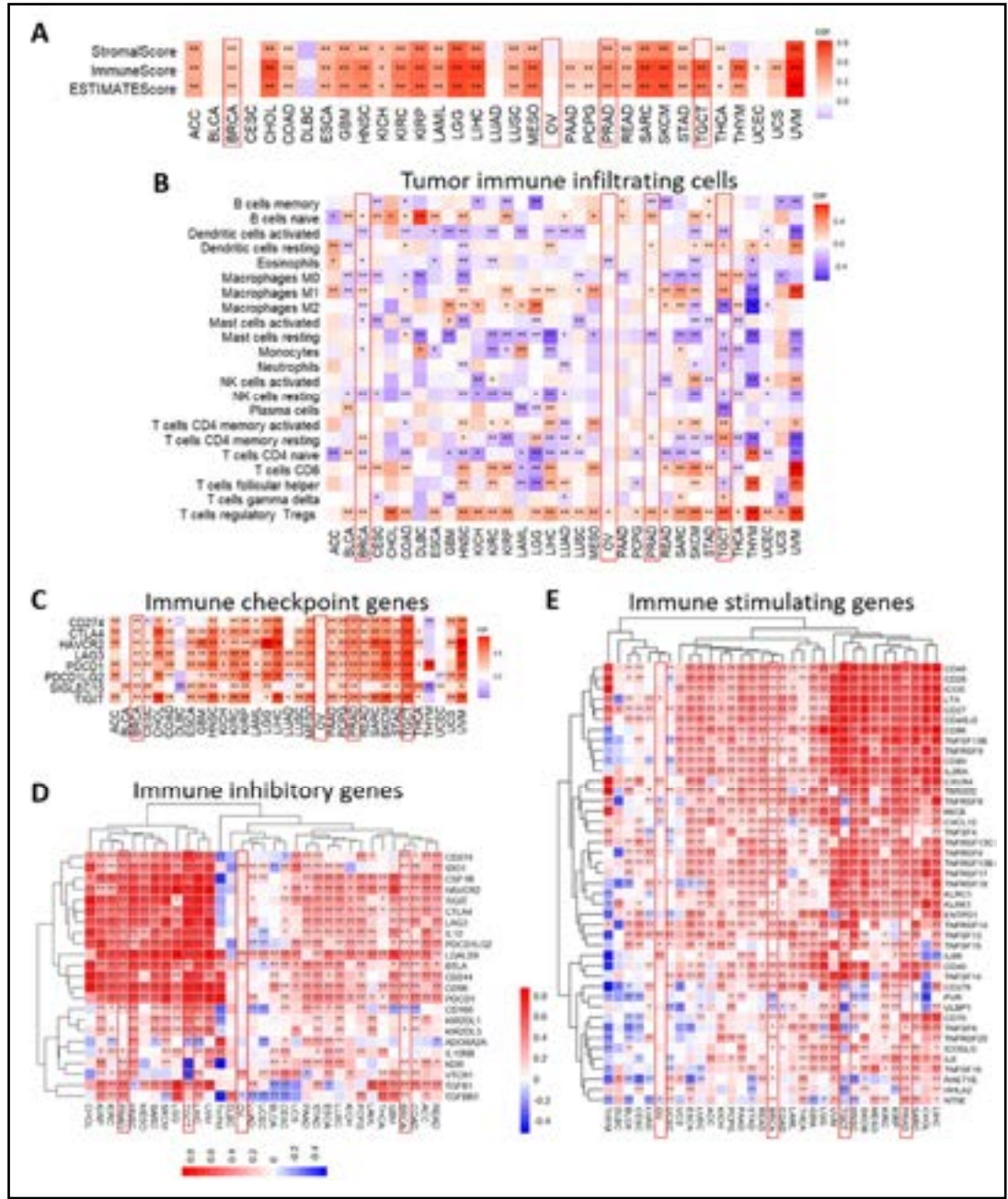Sadeghi et al.: Pan-Cancer Analysis of UCP2 with Sex and Gender Focus

Fig. 4. Correlation between UCP2 expression and immune properties in pan-cancer. (A) Heatmap showing pan-cancer correlation analysis of UCP2 and immune scores, generated using Pearson correlation analysis. (B) Correlation analysis between UCP2 expression and tumor-infiltrating immune cells (TIICs) in 33 cancer types. Pearson correlation analysis was used to calculate the correlation between UCP2 expression and immune cell ratio. (C) Immune checkpoint-associated genes. (D) Immune inhibitory genes. (E) Immune stimulating genes. Similar clusters were identified using the complete linkage method, with significance levels indicated as **$p<0.01$ and *$p<0.05$. The heatmaps were drawn using the TCGAplot R package (v7.0.1) (https://github.com/tjhwangxiong/TCGAplot). Pearson correlation analysis was used to calculate the correlation between UCP2 expression and these immune-related genes.

positively correlated with most immune checkpoint genes in nearly all analyzed tumors. Particularly strong correlations were evident in testicular and prostate cancers. However, moderate associations were found in breast cancer. Interestingly, no significant correlations were observed in ovarian cancer, suggesting that UCP2 may not play a key role in immune regulation within the tumor microenvironment of this cancer type (Fig. 4C).

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Additionally, we investigated the association of *UCP2* with the immune inhibitory (Fig. 4D) and immune stimulatory genes (Fig. 4E), chemokine-related genes, and chemokine receptor genes (Fig. S2A, B). Interestingly, *UCP2* showed strong positive correlations with most immune inhibitory and stimulatory genes in cancers with higher incidence in males, such as kidney renal papillary cell carcinoma (KIRP), kidney renal clear cell carcinoma (KIRC), head and neck squamous cell carcinoma (HNSC), and liver hepatocellular carcinoma (LIHC) (Fig. 4D, E; Table S5). In contrast, the most pronounced negative correlations were observed in cancers such as cervical squamous cell carcinoma (CESC), uterine corpus endometrial carcinoma (UCEC), lung adenocarcinoma (LUAD), and thymoma (THYM) (Fig. 4D, E; Table S5). Accordingly, strong positive correlations between *UCP2* and these genes were found in prostate and testicular cancers, while in breast and ovarian cancer, the correlations were weak or absent. These results suggest that UCP2 may have varying effects on immune characteristics depending on the cancer type and potentially showing a sex-biased incidence.

Correlation analysis of UCP2 expression with steroidogenic and sex hormone receptor genes in gender-related cancers

Sex steroids play crucial roles in various biological processes. However, they can also promote cancer-related characteristics by affecting cell proliferation, migration, and invasiveness. Alterations or malfunctions in the steroidogenic pathway may contribute to the development of cancers, such as breast, ovarian, prostate, and testicular cancer [49, 50, 51, 52, 53]. UCP2 may impact steroid production by affecting mitochondrial function and cellular metabolism [54, 55]. We examined the connection between *UCP2* and several key genes involved in steroidogenesis (Fig. 5A) and identified significant correlations with essential enzymes in sex steroid biosynthesis [56]. In breast cancer (BRCA) and prostate cancer (PRAD), *UCP2* was found to be associated with *CYP11A1*, *CYP19A1*, and *HSD17B2*. A positive correlation between *UCP2* and CYP17A1 was also observed in PRAD and testicular germ cell tumors (TGCT). Furthermore, *UCP2* showed a positive correlation with *HSD3B7* in ovarian cancer (OV) and BRCA (Fig. 5A). Sex steroids exert their biological functions by interacting with specific sex hormone receptors, including estrogen receptors (ESR), progesterone receptors (PGR), and androgen receptors (AR) [57]. Thus, we investigated the correlation between *UCP2* and these genes (Fig. 5B). In BRCA, *UCP2* exhibited slight but statistically significant positive correlations with *ESR1* (R=0.082, p=0.006), *PGR* (R=0.08, p=0.0076), and with *AR* (R=0.27, p<2.2e−16) (Fig. 5C). In OV, *UCP2* was linked with *ESR1* (R=0.21, p=1.3e−05). (Fig. 5C). In both PRAD and TGCT, *UCP2* was associated with *ESR1* (PRAD: R=0.32, p<0.05; TGCT: R=0.36, p=4.1e−06), *ESR2* (PRAD: R=0.15, p<0.05; TGCT: R=0.24, p=0.0025), and PGR (PRAD: R=0.26, p=2.2e−09; TGCT: R=0.25, p=0.0017) but not with *AR* (Fig. 5C). These data indicate that UCP2 expression widely correlates with key steroidogenic genes in cancers and may influence sex hormone pathways by interacting with sex receptor genes.

The multifaceted role of UCP2 in tumor progression and immune modulation in breast (BRCA), prostate (PRAD), ovarian (OV), and testicular (TGCT) cancers

Considering the results showing alterations of *UCP2* expression in various tumor types, its associations with immune characteristics, and its potential involvement in hormone-driven cancers, we further explored its role in breast, prostate, ovarian, and testicular malignancies. Genetic and epigenetic alterations are crucial in tumorigenesis, affecting gene expressions and interfering with key cellular pathways that regulate cellular proliferation and functions [58]. Our analysis revealed distinct differences in the copy number alterations (CNA) of the *UCP2* gene between female and male cancers. A high amplification rate of *UCP2* was found in BRCA and OV, while deletions were mainly observed in TGCT. PRAD showed relatively low levels of both amplifications and deletions (Fig. 6A, B). Furthermore, we investigated the promoter methylation of *UCP2* and revealed significant inverse correlations with *UCP2* expression in BRCA, PRAD, and TGCT. High promoter methylations correlated with reduced *UCP2* expression in these cancers (Fig. 6C). The analysis of copy number variations (CNVs) revealed that amplifications and deletions of *UCP2* affected immune cell infiltration (Fig. 6D). In BRCA, amplifications were associated with an increase in B cells, dendritic (DC) cells, and macrophages, as well as with a decrease in CD4 T and natural killer (NK) cells. On the other hand, deletions were linked to an increment in CD8 naive T cells.
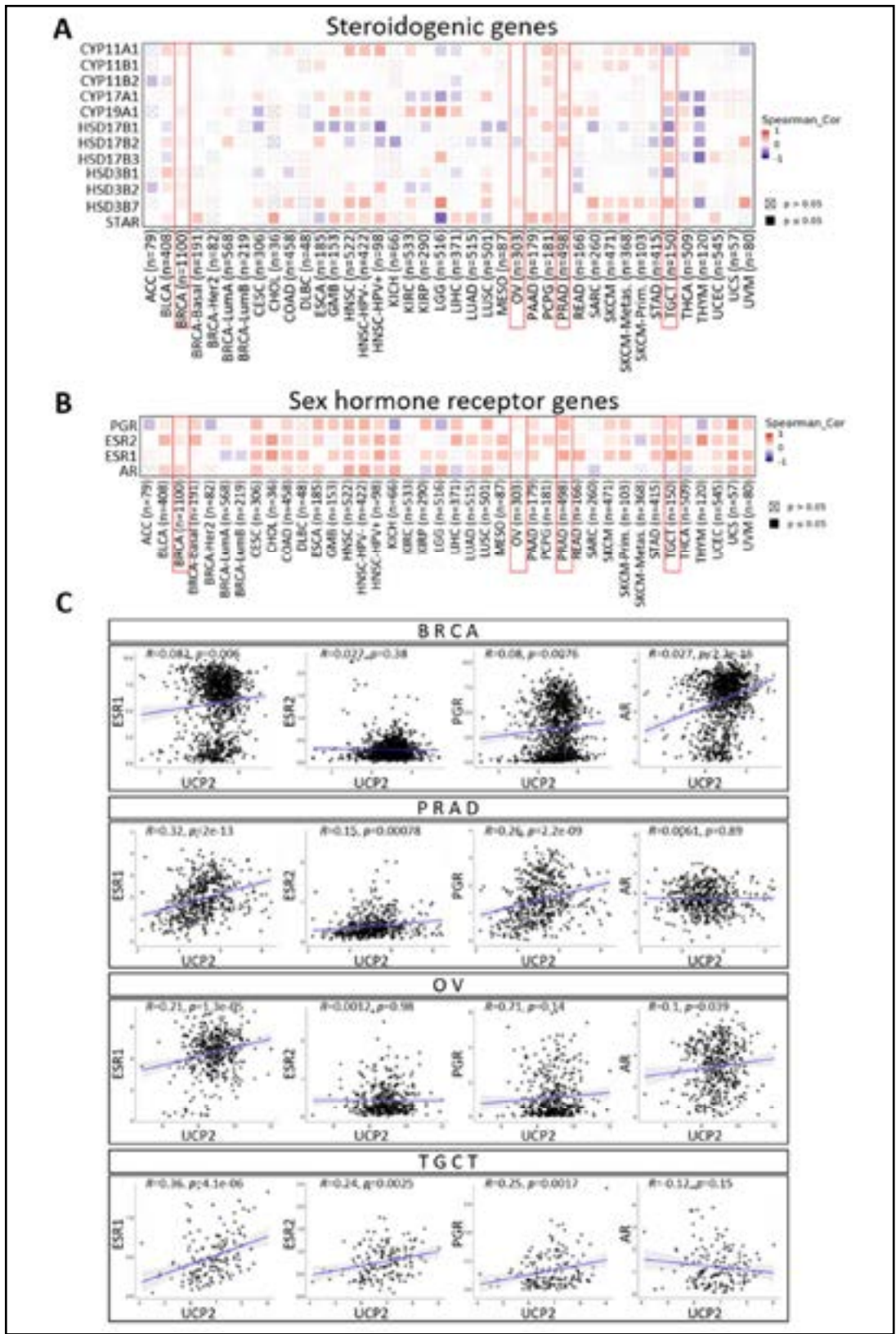
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Fig. 5. Correlation analysis of UCP2 expression with steroidogenic and sex hormone receptor genes. Heatmaps from TIMER2.0 analysis showing pan-cancer correlation analysis of UCP2 and genes related to steroidogenesis (A) and sex hormone receptors (B). The color coding represents the strength and direction of the correlations, with red indicating a positive correlation, blue indicating a negative correlation, and white indicating no correlation. Grey crosses denote non-significant correlations (p > 0.05). (C) Correlation Plots of UCP2 Expression with hormone receptor genes (ESR1, ESR2, PGR, AR) Across Breast, Prostate, Ovarian, and Testicular Cancers by using the TCGAplot R package (v7.0.1) (https://github.com/tjhwangxiong/TCGAplot)

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In OV, amplifications enhanced induced regulatory T cells (iTreg), while deletions, like in breast cancer, increased CD8 naive cells. In PRAD, amplifications increased macrophages, Th1 cells, DC cells, and iTreg cells. Conversely, deletions increased cytotoxic and NK cells but reduced CD4 naive and Th17 cells. In TGCT, deletions, like in PRAD, increased cytotoxic cells (Fig. 6D; Supplementary file 1). *UCP2* is highly expressed in macrophages, predominant immune cells in breast, prostate, ovarian, and testicular tissues (Fig. S3).
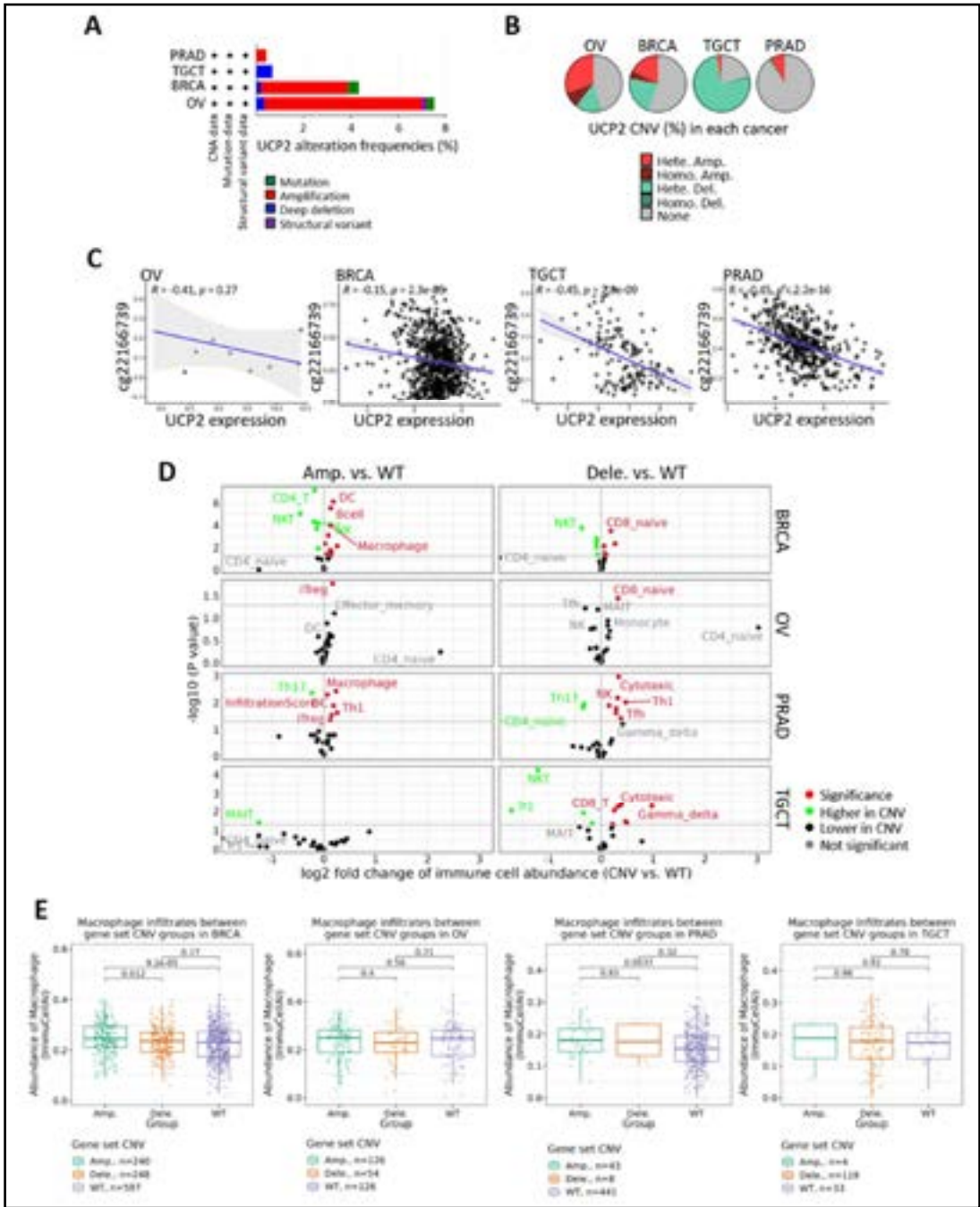

Fig. 6. Mutation and methylation analyses of UCP2 across BRCA, OV, PRAD, and TGCT tumors. (A) Mutation types, frequencies, and sites of UCP2 across cancer types from the cBioPortal. (B) The Gene Set Cancer Analysis (GSCA, http://bioinfo.life.hust.edu.cn/GSCA/#/) was used to define copy number variations (CNVs). (C) Scatter methylation plot (Scatter Pie Plot v0.2.3) showing the correlation between UCP2 expression and promoter methylation in BRCA, PRAD, OV, and TGCT by using the TCGAplot R package (v7.0.1) (https://github.com/tjhwangxiong/TCGAplot). (D) A volcano plot was generated using GSCA, showing the log2 fold change in immune cell abundance between CNV and WT samples. (E) Box plot from GSCA investigating the CNV of UCP2 and macrophage infiltration in BRCA, PRAD, OV, and TGCT.

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Therefore, we aimed to investigate whether variations in the copy number of *UCP2* could impact macrophage infiltration in these cancer types (Fig. 6E). *UCP2* amplifications were correlated with increased macrophage infiltration in BRCA and PRAD but not in OV and TGCT. These data indicate that methylation and copy number alterations (CNAs) impact the expression of *UCP2* and influence the tumor microenvironment (TME). Amplifications in female cancers (BRCA and OV) promote immune cell infiltration and immunosuppressive profiles, while deletions in male cancers (PRAD and TGCT) favor cytotoxic immune responses.

Impact of UCP2 expression and methylation on overall survival in breast (BRCA), prostate (PRAD), ovarian (OV), and testicular (TGCT) cancers

Given the observed impact of *UCP2* alterations on tumor immune microenvironments, we evaluated how *UCP2* expression (Fig. 7A) and methylation signature (Fig. 7B) affect overall survival in breast (BRCA), prostate (PRAD), ovarian (OV), and testicular (TGCT) cancers. Several lines of research investigated the *UCP2* impact on patient survival in breast cancer. Some studies indicated that higher *UCP2* expression was associated with a worse prognosis [59], while others have revealed increased survival [60]. Our data aligns with the studies [61], showing no significant impact of *UCP2* expression on BRCA survival (Fig. 7A). We observed that increased *UCP2* expression correlated with prolonged survival in OV (p=0.043), while it was associated with decreased survival in PRAD (p=0.032) (Fig. 7A). DNA methylation, a critical epigenetic mechanism influencing cancer development and progression, also contributes to patient survival [62]. High DNA methylation at cg22166739UCP2 was associated with decreased *UCP2* expression and was linked to increased overall survival in BRCA patients (p=0.0087). The methylation level of *UCP2* did not affect survival outcomes in OV, PRAD, and TGCT patients (Fig. 7B). To further understand the complex role of *UCP2* and its impact on patient prognosis in these cancers, we conducted an analysis of patient survival using the Kaplan-Meier survival and COX proportional hazards model based on the cancer stage. Considering this variable, high *UCP2* expression was associated with reduced survival in advanced BRCA and TGCT cancer stages (Fig. S4A-D). These results indicate that *UCP2* expression and methylation impact prognostic outcomes, which vary depending on the type of cancer and possible gender-related discrepancies.

Correlation analysis of UCP2 and clinical phenotypes in breast (BRCA), prostate (PRAD), ovarian (OV), and testicular (TGCT) cancers

Patients over 60 showed significantly lower *UCP2* expression in OV. Still, no such reduction was observed in BRCA, PRAD, or TGCT (Fig. 8A). The elevated *UCP2* expression in younger OV patients suggests a potential role for *UCP2* in the early onset or more aggressive forms of the disease. We also evaluated the expression difference of *UCP2* in various tumor stages (Fig. 8B). The analysis did not reveal statistically significant differences in *UCP2* expression across tumor stages of these cancers. However, the available data was insufficient for a conclusive study. In OV, a notable trend of increased *UCP2* expression was observed in the early stages, suggesting that *UCP2* may play a role in the initial phases of tumor development. Conversely, a tendency toward decreased *UCP2* expression in advanced stages of TGCT may indicate a role in tumor suppression as the disease progresses (Fig. 8B). The expression of *UCP2* and its relationship with metastasis varies across different cancer types (Fig. 8C). In BRCA and OV, *UCP2* expression is higher in primary tumor tissues compared to normal tissues. However, its expression decreases during metastasis, although it remains higher than in normal tissues. This indicates that UCP2 may play a dynamic role in early tumor progression but may become less involved as metastasis advances. The expression of UCP2 in PRAD tumors is lower in primary tumors compared to normal tissues and even more reduced in metastatic tumors, suggesting that UCP2 may play a suppressive role in the progression of prostate cancer (Fig. 8C). For TGCT, the available data was insufficient to draw definitive conclusions about *UCP2* expression patterns in metastasis (Fig. 8C). These results indicate that *UCP2* levels are higher in primary BRCA and OV tumors but lower in primary tumors of PRAD. *UCP2* levels decrease during metastasis in both female (BRCA, OV) and male (PRAD) cancers, although this decline is more consistent in PRAD.
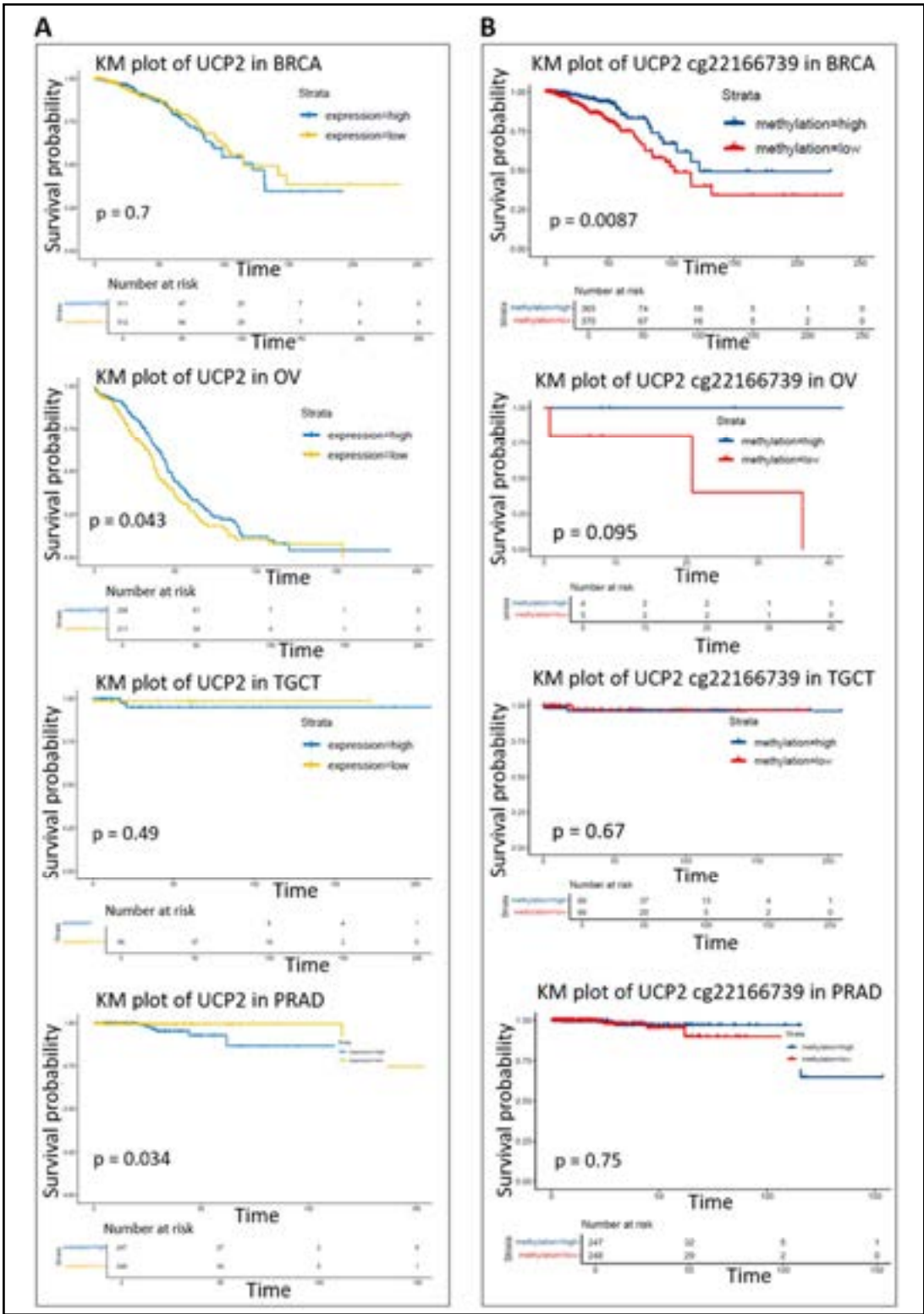
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Fig. 7. Kaplan-Meier (KM) analysis. (A) KM analysis examining the correlation between UCP2 expression and overall survival (OS) in patients with BRCA, PRAD, OV, and TGCT. (B) KM analysis investigating the correlation between UCP2 methylation and OS in BRCA, PRAD, OV, and TGCT patients. The KM plots were generated using the TCGAplot R package (v7.0.1) (https://github.com/tjhwangxiong/TCGAplot).

The potential functions of UCP2 in breast (BRCA), prostate (PRAD), ovarian (OV), and testicular (TGCT) cancers

We examined the correlation between *UCP2* and other differentially expressed genes (DEGs) in BRCA, PRAD, OV, and TGCT cancers (Fig. 9A-D, Fig. S5 A-D), revealing several significant findings. Among the top 20 positively correlated genes in the heatmaps (Fig. 9A-D), *GPSM3* was consistently identified across BRCA, PRAD, and TGCT (Fig. 9A, B, D). *GPSM3* has been identified as a prognostic and immunological biomarker in several cancers. It is mainly expressed in myeloid cells, playing crucial roles in regulating migration and inflammatory responses of these cells [63, 64, 65]. In BRCA and PRAD, *UCP2* expression was significantly associated with two critical immune-related genes: *CD74* and *LGAL9* (Fig. 9A, B). *CD74* is known to function as a receptor for macrophage migration inhibitory factor (MIF) and plays a pivotal role in antigen processing and immune responses [66, 67]. *LGAL9* (galectin-9), on the other hand, is involved in immune regulation by modulating T-cell activity and contributing to immune tolerance [68, 69]. These findings suggest that *UCP2* plays significant roles in immune activation and regulation in both male and female cancers, acting through critical immune modulators like GPSM3, CD74, and LGAL9.

Fig. 8. Pan-cancer correlation analysis of UCP2 and clinical phenotypes. (A) Expression of UCP2 in patients aged ≤ 60 and > 60 years in BRCA, PRAD, OV, and TGCT. The Wilcoxon test was used for comparisons. (B) Correlation of UCP2 expression with BRCA, OV, and TGCT tumor stage. Data is shown as log2(TPM + 1), and the Wilcoxon test was used to compare different groups. ns indicates no significant difference. (C) Correlation of UCP2 expression with primary and metastatic tumors in BRCA, PRAD, and OV.

In BRCA, gene ontology (GO) enrichment showed that *UCP2* was involved in regulating leucocyte chemotaxis. GO enrichment from the GSEA database indicated that high *UCP2* expression participated in the adaptive immune response and immune response regulating cell surface receptor signaling. GSEA-KEGG indicated *UCP2* participation in cytokine-cytokine receptor interaction (Fig. 9A). In PRAD, GO enrichment associated *UCP2* with leucocyte cell-cell adhesion. GSEA-GO analysis revealed that *UCP2* was associated with the adaptive immune response (Fig. 9B). In OV, GSEA-GO analysis associated high *UCP2* expression with improved cell-killing pathways, and GSEA-KEGG analysis connected *UCP2* to immune response pathways, such as those involved in Epstein-Barr virus infection and NOD-like receptor signaling (Fig. 9C). In TGCT, leucocyte cell-cell adhesion genes were among the UCP2 positively co-expressed genes in GO. GO database from GSEA enrichment showed that UCP2 participated in the adaptive immune response, antigen receptor-mediated signaling pathway, immune response activating cells surface receptor signaling, leucocyte-mediated immunity, and lymphocyte-mediated immunity (Fig. 9D).
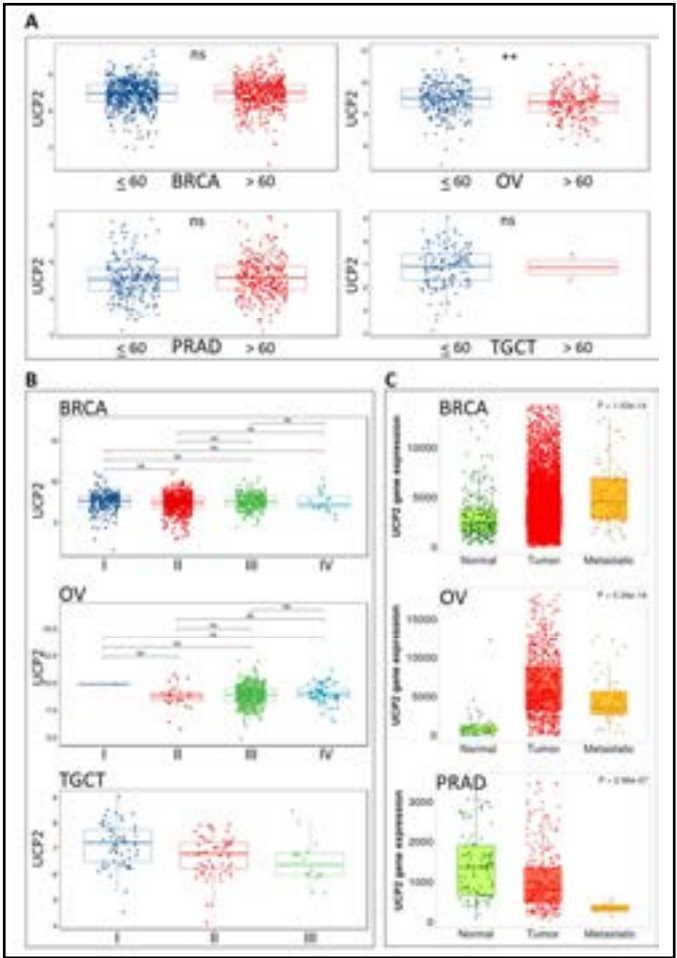
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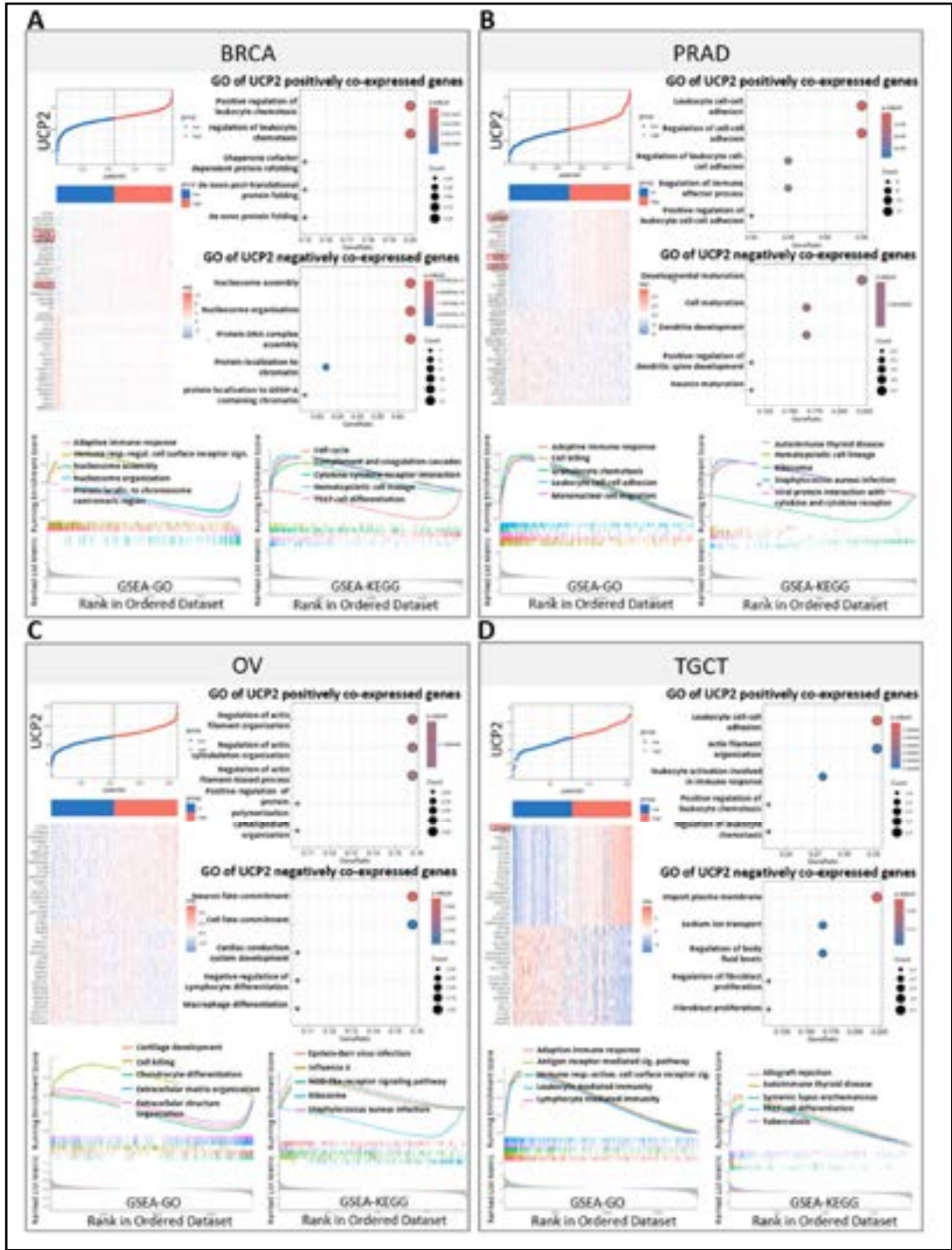

Fig. 9. DEGs analysis, GO analysis, GSEA-GO analysis, and GSEA-KEGG analysis in BRCA, PRAD, OV, and TGCT. Expression heatmap and enriched Gene Ontology (GO) pathways of genes significantly positively or negatively correlated with UCP2 in patients with BRCA (A), PRAD (B), OV (C), and TGCT (D). GSEA-GO and GSEA-KEGG analyses were conducted. Pearson correlation analysis was used to calculate the correlation between UCP2 expression and immune-related genes. Similar clusters were identified using the complete linkage method. Significance levels are indicated as **p<0.01 and *p<0.05. The heatmap was drawn using the TCGAplot R package (v7.0.1) (https://github.com/tjhwangxiong/TCGAplot).

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In addition, the analysis of *UCP2* gene expression across these cancers revealed significant roles in multiple biological pathways. In breast cancer, *UCP2* was associated with the Apoptosis, cell cycle, EMT, RTK, and PI3KAKT pathways, suggesting its influence on cell death, growth, and migration. In ovarian cancer, *UCP2* negatively correlated with the EMT pathway, possibly affecting metastasis. In prostate and testicular cancers, *UCP2* played a crucial role in hormone signaling, cell growth, and survival, particularly in the Hormone ER, PI3KAKT, TSCmTOR, and DNA damage pathways, indicating its broad involvement in cancer progression and regulation (Fig.S5E, Supplementary file 2). These data suggest that UCP2 is implicated in immune regulation, influencing immune-related pathways with significant associations observed in both male and female cancers.

UCP2 expression predicts drug sensitivity
Understanding the susceptibility of cancer cells to antineoplastic drugs is essential for developing effective anticancer therapies. The correlation between UCP2 and drug sensitivity was investigated in CTRP and GDSC databases using the Gene Set Cancer Analysis (Fig. 10A, B, Supplementary file 3). Drugs targeting critical oncogenic pathways and epigenetic regulators, including LRRK2, histone deacetylase, PI4KIIβ, and BET proteins, were negatively correlated with UCP2. On the other hand, UCP2 expression was positively correlated with seven specific drugs, such as 17-AAG, bleomycin, docetaxel, PD-0325901, RDEA119, selumetinib, and trametinib. These results indicate that *UCP2* expression may predict treatment outcomes.
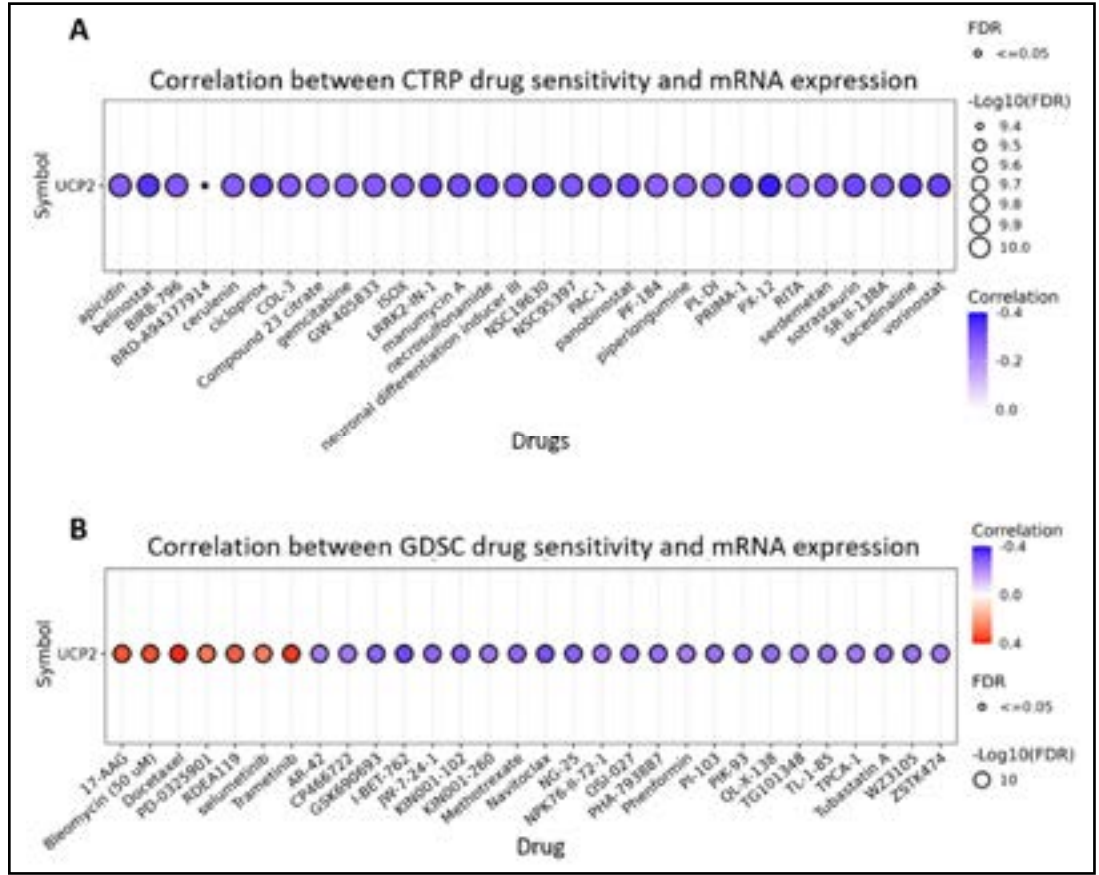

Fig. 10. UCP2 Expression Predicts Drug Sensitivity. (A) Correlation between UCP2 expression and the top 30 CTRP drug sensitivities in pan-cancer. (B) Correlation between UCP2 expression and the top 30 GDSC drug sensitivities in pan-cancer.

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Discussion

Excessive ROS accumulation can trigger cancer by altering cellular metabolism and immune responses, enabling cancer cells to survive, multiply, and spread to other body parts. In this context, UCP2, known for its various functions in regulating oxidative stress and metabolism, emerges as a potential biomarker and therapeutic target in cancer. Depending on the type of tumor, its metabolic status, and its stage, UCP2 could be strategically targeted by either inhibiting or activating it to influence cancer outcomes [30]. In this study, we comprehensively examined the distinct characteristics of UCP2. This included analyzing its expression, genomic mutations, instability, prognosis, association with immune infiltration, and relationship with steroidogenic and sex receptor genes in human cancer, with a particular emphasis on hormone-driven cancers, such as breast (BRCA), prostate (PRAD), ovarian (OV), and testicular (TGCT) cancers.

UCP2 levels vary across cancer types, reflecting different functions and metabolic tumor characteristics [25],[26]. Our results showed that *UCP2* was elevated in BRCA and OV, while reduced levels were observed in PRAD and TGCT, suggesting a potential sex-specific influence of UCP2 in these cancers. In addition to PRAD, reduced *UCP2* expression was found in some cancers, with a higher incidence in males. These involve kidney chromophobe (KICH), lung squamous cell carcinoma (LUSC), and pancreatic adenocarcinoma (PAAD) (Table S5), [70, 71, 72]. Conversely, cancers such as BRCA, thyroid cancer (THCA), lung adenocarcinoma (LUAD), and uterine corpus endometrial carcinoma (UCEC) showed upregulated *UCP2* levels and are more prevalent in females (Table S5). These results indicate that the expression of *UCP2* plays a dual and context-dependent role in cancer, with potential gender-specific influence, highlighting the complexity of the UCP2 function and the need for further research. UCP2 plays a crucial role in regulating mitochondrial function, controlling ROS generation, and contributing to chemoresistance [73, 74, 17, 59]. UCP2 functions as a survival enhancer for various cancer cells, contributing to treatment resistance, and resulting in poor patient outcomes [60],[75], [76]. However, it may also, in specific contexts, be associated with improved prognosis [77], suggesting its involvement in distinct molecular mechanisms. The prognosis analysis presented in this study further underscores the dual role of UCP2 in hormone-related cancers such as breast, prostate, ovarian, and testicular cancers. *UCP2* expression was associated with prolonged survival in ovarian cancer while contributing to reduced lifespan in prostate cancer.

The differences in *UCP2* expression based on gender and their connection to survival indicate that sex hormones or related pathways may play a role in regulating UCP2 activity in cancer. For example, UCP2 has been identified as a risk factor in cancers with reduced UCP2 levels (Table S2), such as kidney renal papillary cell carcinoma (KIRP), acute myeloid leukemia (LAML), and lower-grade glioma (LGG), which are more common in males (Table S5) [70, 78, 79]. Conversely, *UCP2* predicted a better prognosis in cervical squamous cell carcinoma (CESC), lung adenocarcinoma (LUAD) [80], and OV. These malignancies exhibit upregulated *UCP2* expression (Table S2) and are exclusively or more frequent in females (Table S5).

UCP2 gene amplification has been found in several hormone-driven cancers, with its polymorphism associated with increased disease risk [21],[22]. Our analysis showed dominant *UCP2* amplifications in OV and BRCA and deletions in TGCT, indicating that UCP2 may play a distinct role in the oncogenic processes of these cancers and emphasize its potential involvement in gender-related tumor progression.

The connection between *UCP2* and key immunotherapy biomarkers, such as tumor mutational burden (TMB) and microsatellite instability (MSI) [81], demonstrates its potential influence on tumor immunogenicity. Specifically, *UCP2* showed a positive correlation with TMB in OV and a negative association with MSI in TGCT, suggesting that it could be a predictive biomarker for immunotherapy effectiveness in these malignancies.

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UCP2 has been implicated in shaping the tumor microenvironment (TME), particularly in breast and melanoma cancers, through the modulation of immune cell infiltration and therapy resistance [60, 82]. Our data from breast, prostate, ovarian, and testicular cancer analysis revealed that *UCP2* correlated with immune cell populations involved in immune evasion. The copy number variations (CNVs) of *UCP2* significantly affected immune cell composition, particularly macrophages, T cells, and regulatory T cells in these cancers. Amplifications of *UCP2* were correlated with increased macrophage infiltration in breast and prostate cancers. In breast cancer, *UCP2* amplifications also increased B cell and dendritic cell infiltration, suggesting an anti-tumor inflammatory environment. Meanwhile, in prostate cancer, increased iTregs indicated a pro-tumor inflammatory environment.

In contrast, the deletions of *UCP2* were linked to increased cytotoxic T cells in prostate and testicular cancers, promoting anti-tumor immunity. The consistent association between *UCP2* expression and immune response pathways, including adaptive immunity, immune receptor signaling, leukocyte adhesion, immune cell migration, and immune activation, further supports the role of UCP2 in coordinating immune-related processes and influencing the TME.

Gender-related cancers are highly influenced by sex hormones, and disruption in steroidogenic pathways can lead to the development and progression of tumors [83]. *CYP11A1*, *CYP19A1*, and *HSD17B2* are crucial enzyme genes in steroidogenesis, playing important roles in the biosynthesis of sex hormones such as estrogen and testosterone [84, 85, 86]. Changes in these enzymes are frequently observed in sex-dependent cancers, contributing to an imbalance in hormone production and regulation that drives tumor progression. *UCP2* displayed strong positive correlations with these genes in breast and prostate cancer, potentially affecting cancer development and progression through its interaction with steroid hormone synthesis pathways. In addition, the correlation of *UCP2* with estrogen and progesterone receptor genes in breast, ovarian, prostate, and testicular cancers, indicates a broader influence on hormone receptor signaling. Interestingly, the absence of a significant correlation between *UCP2* and androgen receptor genes in male cancers suggests that UCP2 may have a more prominent role in estrogen than androgen receptor pathways. These findings highlight the context-dependent influence of UCP2 on steroid metabolism and hormone receptor activity, with potential implications for targeted therapeutic strategies.

Moreover, our analysis demonstrated that *UCP2* expression predicts drug sensitivity, with high *UCP2* levels correlating with resistance to several oncogenic therapies but increased sensitivity to agents such as 17-AAG, docetaxel, bleomycin, selumetinib, and trametinib. This suggests these drugs may be particularly effective in tumors with elevated UCP2 levels and combining them with UCP2 inhibitors could enhance cancer treatment. However, specific UCP2 inhibitors are not yet available for clinical use. Additionally, *UCP2* involvement in steroidogenesis and hormone receptor signaling, particularly in hormone-dependent cancer, highlights the need to consider other combination therapies. In these cases, combining hormone-targeting treatments with UCP2-sensitive drugs may offer a more effective approach. For example, in breast and ovarian cancers, combining endocrine therapies (e.g., tamoxifen, aromatase inhibitors) with UCP2-sensitive drugs (e.g., docetaxel or 17-AAG) can target hormone receptor signaling and enhance cancer cell death [87, 88, 89, 90, 91]. In resistant cases, selective receptor degraders (SERDs; e.g., fulvestrant) combined with MEK inhibitors (e.g., trametinib or selumetinib) could address the UCP2-driven resistance mechanism [92][93]. In prostate and testicular cancers, *UCP2* did not correlate with androgen receptors, so alternative pathways should be targeted. Combining CYP17A1 inhibitors (e.g., abiraterone) with MEK inhibitors could target both steroidogenesis and MAPK signaling [94]. Alternatively, estrogen receptor antagonists paired with UCP2-sensitive drugs [95, 96] may further improve outcomes in hormone receptor-positive, UCP2-high tumors. In addition to hormonal pathways, our findings indicate a link between *UCP2* expression and immune checkpoint genes, suggesting another potential approach for combined therapy. Combining immunotherapies, such as PD-L1 or CTLA-4 inhibitors, hormone therapies (estrogen or androgen blockade), and UCP2-sensitive drugs, such as 17-AAG, could be a way to improve treatment strategies for tumors with high UCP2 expression.

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Strengths and Limitations of Data Sources

This study used large-scale databases such as TCGA, cBioPortal, and GSCA to investigate UCP2 expression and its implications in cancer. These databases provide extensive genomic, transcriptomic, and clinical datasets, allowing for comprehensive multi-omics analyses across various types of cancer. Such an integrative approach is essential for identifying new biomarkers and therapeutic targets, such as UCP2, contributing to advances in precision oncology. TCGA has played a crucial role in discovering key oncogenes and tumor suppressors, which has, in turn, facilitated the development of targeted cancer therapies. Similarly, the GSCA has provided valuable insights into the relationship between gene expression, such as UCP2, and drug sensitivity, advancing more tailored and individualized treatment strategies. However, it is essential to consider several limitations. The lack of important clinical information, such as survival outcomes, cancer staging, and treatment regimens, limited the analysis. Moreover, genetic variations in non-coding, crucial for gene regulation and disease progression, were underrepresented. The lack of data on non-coding RNA, which plays a pivotal role in cancer-related gene regulation, further limited the ability to fully explore regulatory mechanisms such as those involving *UCP2*. Additionally, the lack of healthy control data and precise drug dosage information complicated the ability to conduct rigorous comparative analyses. Future research should prioritize integrating more comprehensive datasets, including clinical, regulatory, and pharmacological data, to enhance understanding of the oncogenic role of UCP2 and to optimize therapeutic approaches accordingly.

Conclusion

In conclusion, we conducted a comprehensive pan-cancer analysis of UCP2. The study revealed significantly increased *UCP2* expression in most TCGA cancers, including breast, while observing markedly decreased expression in certain cancers, such as prostate cancer. We have demonstrated a potential correlation between UCP2 and prognosis in certain cancers. Additionally, we have identified a possible link between the prognostic significance of *UCP2* expression and TMB, MSI, immune infiltration, and genes associated with immunotherapy. UCP2, indeed, is highly expressed in immune cells. Therefore, it is worth noting that there is a limitation in the dataset analysis, as it does not allow us to distinguish whether *UCP2* expression originates from tumor cells or immune cells. Thus, additional research is required to clarify whether the observed *UCP2* expression influences prognosis through its impact on cancer cell behavior or the increased presence of UCP2-expressing immune infiltrates. Finally, the involvement of UCP2 in shaping the tumor microenvironment, including its positive correlation with macrophage infiltration and immune-related pathways, highlights its potential to promote anti-tumor immune responses. Conversely, its reduced expression in cancers like the prostate and its association with worse prognosis in some contexts indicate its complex role in tumor biology, potentially linked to sex-specific mechanisms and hormonal pathways. Estrogens and androgens can regulate mitochondrial biogenesis, oxidative stress responses, and metabolic functions, all of which are tightly linked to UCP2 activity. These hormones might influence how *UCP2* is amplified or deleted and its functional impact in different cancers. Understanding how sex hormones could modulate UCP2 expression and its genetic alterations and whether to which extent UCP2 affects sex hormone levels could provide insights into sex-specific cancer therapies and the distinct metabolic vulnerabilities of cancers in men versus women.

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Statement of Ethics

The authors have no ethical conflicts to disclose

Disclosure Statement

The authors have no conflicts of interest to declare

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