Correlateions between UBE2T Expression and Immune Infiltration in Different Cancers

Yunliang Yu[1][a] and Ting Li[2][b]
[1]Department of Medical Laboratory, Yantai Affiliated Hospital of Binzhou Medical University, Yantai, Shandong, 264100, China
[2]Department of Pathology, Yantai-Mountain Hospital of Yantai, Yantai Shandong, 264000, China

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Abstract: Ubiquitin-conjugating Enzyme E2T (UBE2T) has been implicated in the development of several cancers. However, the interaction of UBE2T and cancer immunity in many tumors remains uncertain. In this study, we looked at the clinicopathological importance of UBE2T in various malignancies, as well as the links between UBE2T and prognosis and tumor-infiltrating lymphocytes in a variety of cancers. The Gene Expression Profiling Interactive Analysis (GEPIA) and Tumor Immune Estimation Resource (TIMER) databases were used to extract UBE2T expression data. The Kaplan-Meier plotter and the GEPIA databases were used to evaluate the relationship between UBE2T expression and cancer patients' clinical prognosis. TIMER was used to look for relationships between UBE2T expression levels and tumor-infiltrating cells as well as gene marker sets of immune infiltrates. The findings demonstrated that increased UBE2T expression was substantially related to poor overall survival in individuals with breast cancer or lung adenocarcinoma. In thymoma, stomach carcinoma, and ovarian cancer, patients with a higher UBE2T expression had a better prognosis than those with low expression. Furthermore, elevated UBE2T expression impacted the prognosis of lymphatic metastasis in individuals with breast, lung, and stomach cancer. There were clear positive or negative relationships between UBE2T expression and immune cell infiltration in lung, stomach, and thymoma cancers. Finally, UBE2T may be valued for its dual role in human malignancies because it may play a significant role in the recruitment and modulation of immune infiltrating cells in tumors.

1 INTRODUCTION

Despite breakthroughs in early diagnosis and intervention, cancer remains the leading cause of death globally. It is generally recognized that tumor immune microenvironment (TIME) influences cancer patients' malignancy grade and prognosis (Julia 2017). Numerous studies have found that immune-related systems play important roles in a variety of human malignancies, and tumor immunotherapy has changed cancer treatment (Gorabi 2020). Although immunotherapeutic techniques are thought to be a successful approach for cancer treatment, immunotherapy using anti-PD-1 antibodies and anti-PD-L1 demonstrated a partial response in advanced lung and gastric cancer (Dermani 2019, Bernatchez 2013, Ninomiya 2018). Furthermore, the total immunogenicity of gastric cancer is rather low, and the efficacy of immunological therapy is rather restricted (Lordick 2017). Because breast cancer is also an immunostimulatory illness, some individuals benefit from immunotherapy; nonetheless, it has historically proved resistant to immunotherapy (Pusztai 2016). As a result, it is crucial to investigate the immunodepressive mechanism or immunostimulatory functions in cancer patients in order to uncover novel therapeutic targets for immunotherapy of various tumors. Immune infiltrates can influence tumor patients' prognosis and responsiveness to treatment. Tumor infiltrating lymphocytes (TILs) are commonly regarded as a critical indicator of the immunological interaction here between host and tumor, as well as possible prognostic indicators of good or worse prognosis in invasive malignancies (Baxevanis 2019). Understanding the interplay between the tumor and

[a] https://orcid.org/0000-0001-5450-160X
[b] https://orcid.org/0000-0002-2140-2952

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the host immune system is thus crucial for discovering prognostic biomarkers, limiting medication resistance, and creating novel diagnostic methods.

Ubiquitin-conjugating Enzyme E2T (UBE2T) was first identified in a case of Fanconi anemia. UBE2T functions by combining with specifc E3 ubiquitin ligase to induce the degradation of functional changes in substrate molecules. UBE2T is increasingly recognized as a critical factor during carcinogenesis in human nasopharyngeal, liver, prostate, breast, gastric, lung cancers and so on. Recent evidence also demonstrates that mutations or impairment of the E2s can lead to severe disease states, including chromosome instability syndromes, cancer predisposition, and immunological disorders (Ben-Neriah 2002). It has been observed that UBE2T is increased in breast cancer and that suppressing UBE2T expression can decrease breast cancer cell invasion and metastasis. UBE2T was also shown to be overexpressed in non-small cell lung cancer (NSCLC) tissues and cell lines. In vitro, UBE2T knockdown inhibited NSCLC cell proliferation, migration, and invasion. It was also shown that elevated UBE2T expression was associated with poor differentiation and prognosis in patients with gastric cancer. By modifying the expression of epithelial-mesenchymal transition (EMT)-related factors, suppressing UBE2T expression might reduce the invasive and metastatic properties of gastric cancer cells. Because a vast number of studies have shown that inflammatory T cells, dendritic cells (DCs), monocytes, and macrophages increase tumor metastasis, it is possible that UBE2T is associated with carcinogenesis and immune infiltration in many malignancies.

The goal of this study is to look at the relationship between UBE2T expression and the clinicopathological importance of cancer patients in databases including GEPIA, Kaplan-Meier plotter, and TIMER. The relationship between UBE2T and tumor-infiltrating immune cells in various tumor microenvironments was also thoroughly investigated utilizing the TIMER database. Furthermore, this study looked at the link between the expression pattern of UBE2T and various genes associated with immune regulation in many malignancies for the first time. This study not only demonstrated the significance of UBE2T in malignancies, but it also provided probable linkages and methods of interaction between UBE2T and tumor immunity in thymoma, breast, lung, and gastric cancers.

2 MATERIALS AND METHODS

2.1 GEPIA 2.0 Dataset

GEPIA (http://gepia.cancer-pku.cn/index.html) is an interactive web site that analyzes RNA sequencing expression data from 97,366, tumors and 8,587 normal samples from the TCGA (The Cancer Genome Atlas) and the Genotype-Tissue Expression (GTEx) projects. GEPIA was primarily employed in this investigation to investigate the predictive influence of UBE2T on overall survival (OS) and disease-free survival (DFS) (DFS).

2.2 Kaplan Meier-Plotter Dataset

The Kaplan Meier-plotter database can examine predictive values of gene mRNA expression in patients with breast, gastric, lung, and ovarian cancer, as well as miRNA expression in patients with liver and breast cancer (http://kmplot.com/analysis/). Using the Kaplan Meier-plotter database, we investigated the relationship between UBE2T expression and prognosis in breast, lung, stomach, and ovarian cancer. By comparing the E-MTAB-365 and Gene Expression Omnibus (GEO) datasets, we also confirmed whether UBE2T expression impacts the prognosis of breast, lung, and gastric cancer in patients with lymphatic metastases (dataset: GSE30219 and GSE62254). The Kaplan Meier-plotter dataset included the UBE2T expression and OS rates, RFS (relapse-free survival) rates, progression-free survival (PFS) rates and post-progression survival (PPS) rates of 426 patients with breast cancer (dataset: E-MTAB-365), 307 patients with lung cancer (dataset: GSE30219), 300 patients with gastric cancer (dataset: GSE62254) and 285 patients with ovarian cancer (dataset: GSE9891).

2.3 TIMER Database Analysis

TIMER is an online resource server for systematic analyses of tumor-infiltrating immune cells in various cancer types (https://cistrome.shinyapps.io/timer/). The TIMER platform was utilized in this study to detect distinct profiles of immune cells and to calculate the immunological estimate of the TCGA dataset. These immune cells include B cells, CD4+ T cells, CD8+ T cells, neutrophils, macrophages, and DCs. The gene module on TIMER demonstrated a link between UBE2T expression and varied degrees of immune infiltration. Furthermore, correlations between UBE2T expression and gene markers of tumor-infiltrating immune cells were also explored

by correlation modules. Correlation modules were also used to investigate connections between UBE2T expression and gene biomarkers of tumor-infiltrating immune cells. The correlation method generates expression scatter plots between two user-defined genes in a specific cancer type, where the x-axis indicates relevant marker genes and the left y-axis represents UBE2T. For all correlation graphical representations, Spearman rank correlation was employed.

2.4 Statistical Analysis

A one-sided Student's t-test was used to obtain P-values and fold-changes for UBE2T expression from the GEPIA database. GEPIA and Kaplan-Meier survival plots were used to assess the survival rates estimated from the date of diagnosis. The outcomes of Kaplan-Meier plots and GEPIA are represented as Hazard ratios (HR) and P-values or Cox P-values from a log-rank test. Because associations can be positive or negative, the absolute values of the correlation coefficients in TIMER were used to determine the strength of Spearman rank correlation. A statistically significant difference was defined as one with a value of $P<0.05$.

3 RESULTS

3.1 UBE2T Gene Was Ubiquitously Overexpressed in Tumor Tissue TIMER Database Analysis

Using TIMER-generated RNA-sequencing (RNA-Seq) data from multiple malignant tumors in the TCGA, we investigated at UBE2T expression. The UBE2T mRNA expression was proven to increase dramatically in BLCA (bladder urothelial carcinoma), BRCA (breast invasive cancer), CHOL (cholangio carcinoma), COAD (colon adenocarcinoma), ESCA (esophageal carcinoma), HNSC (head and neck cancer), KICH (kidney chromophobe), KIRC (kidney renal clear cell carcinoma), KIRP (kidney renal papillary cell carcinoma), LIHC (liver hepatocellular carcinoma), LUAD (lung adenocarcinoma), LUSC (lung squamous cell carcinoma), PRAD (prostate adenocarcinoma), READ (rectum adenocarcinoma), STAD (stomach adenocarcinoma), THCA (thyroid carcinoma) and UCEC (uterine corpus endometrial carcinoma) compared with adjacent normal tissues. We also discovered that UBE2T was widely expressed in practically all cancer types, including breast, lung, ovarian, and stomach cancers, after digging further into the GEPIA database. In the same way, UBE2T expression was elevated in distinct BRCA subtypes, LUAD, and LUSC.

3.2 High UBE2T Expression Was Significantly Related to the Prognosis of Tumors

The GEPIA database was used to investigate the links between UBE2T expression and cancer patient prognosis. In many common cancer types, higher expression of UBE2T was associated with a poorer or better survival rate, including ACC (adrenocortical carcinoma), DLBC (diffuse large B-cell lymphoma), KICH (kidney chromophobe), KIRC, KIRP, LGG (lower grade glioma), LIHC, MESO (mesothelioma), PAAD (pancreatic adenocarcino (uveal melanoma). Among them, we found that high UBE2T expression was marginally associated with poor prognosis in BRCA (OS Logrank P=0.017) and LUAD (OS Logrank P=0.001; DFS Logrank P=0.0091). There was no significant relevance between UBE2T expression and prognosis of cancer patients in LUSC. However, high expression level of UBE2T was associated with better prognosis in STAD (DFS Logrank P = 0.04), THYM (thymoma) (OS Logrank P=0.005) and OV (ovarian serous cystadenocarcinoma) (OS Logrank P=0.011). Such differences are suggestive of UBE2T may demonstrate a dual role in the malignant tumor development process. Meanwhile, high expression of UBE2T was found to be related to different tumor stages in BRCA (P=3.34e-5), LUAD (P=0.00164) and OV (P=0.0107). Nevertheless, this correlation was not found in LUSC or STAD.

3.3 High Expression of UBE2T Influences the Prognosis of Breast, Lung and Gastric Cancer in Patients with Lymphatic Metastasis

We used the Kaplan Meier-plotter database to study the predictive functions of UBE2T in breast, lung, and gastric cancer patients in attempt to comprehend the independent influence of UBE2T expression on survival. We discovered that greater UBE2T mRNA expression was linked to a poorer RFS in breast cancer (P=0.0028) and lung cancer (Logrank P=3.3e-7). However, the significant of UBE2T mRNA levels were associated with better OS and PPS in gastric cancer (OS Logrank P=3.7e-5; PPS Logrank P=1.4e-

6) and ovarian cancer (PFS Logrank P=0.011). These results are consistent with our above results.

In the TNM staging system, the N category relates to lymph node involvement; N0 indicates no regional lymph node metastasis, whereas N1-N3 indicate regional lymph node metastasis. We discovered that greater UBE2T expression was linked with poorer RFS in lymph node positive breast cancer patients (P=0.0043), but not with RFS in lymph node negative cancer patients. In lung cancer patients, increased UBE2T mRNA expression was linked with poorer OS in stage N0 (P=0.0067) and stage N2 (P=0.033), but not with OS in stage N1 (P=0.2343). In gastric cancer, elevated UBE2T mRNA expression was linked with a better prognosis in stage N0 (OS P=0.0017; PPS P=0.001) and stage N1 (OS P=0.002; PPS P=0.0011) patients but not in stage N2 (OS P=0.153; PPS P=0.13) and stage N3 (OS P=0.2084; PPS P=0.079) patients. To summarize, our findings suggest that elevated UBE2T expression may affect the prognosis of patients with lymph node metastases in breast, lung, and gastric cancer.

3.4 UBE2T Expression Is Correlated with Immune Infiltration Level in LUAD, STAD And THYM

We predicted that because tumor-infiltrating lymphocytes are an independent predictor of lymph node status and prognosis in malignancies, immunity in tumors may be connected to UBE2T expression. We looked at the relationships between UBE2T expression and TIL quantity as measured by tumor purity. TIMER examined the relationship between UBE2T expression and immune infiltration levels in 39 cancer types. Higher UBEB2T expression was shown to be substantially linked with tumor purity in 27 different forms of cancer. Furthermore, patients with greater UBE2T expression demonstrated considerable infiltration of CD8+ cells in 7 cancer types, CD4+ T cells in 28 cancer types, macrophages in 25 cancer types, neutrophils in 18 cancer types, and DCs in 19 cancer types. Among these, UBE2T expression is linked to varying amounts of immune infiltration and tumor purity in BRCA, LUAD, STAD, and OV. Furthermore, in breast cancer, there were very moderate relationships between UBE2T expression and infiltrating quantities of B cells and CD4+ T cells. The degree of UBE2T expression infiltrating B cells, CD4+ T cells, macrophages, neutrophils, and DCs revealed significant negative correlations in LUAD. B cells, CD8+ cells, CD4+ T cells, macrophages, neutrophils, and DCs infiltrated less frequently in UBE2T overexpression instances in STAD. However, in ovarian cancer, there was almost no association between UBE2T expression and immune cell infiltration levels. Surprisingly, the infiltrating levels of B cells, CD8+ T cells, CD4+ T cells, macrophages, and DCs have higher substantial positive relationships with UBE2T expression levels in THYM.

In general, this then implies that UBE2T may be implicated in immune infiltration in thymoma, lung and gastric cancer, especially those of CD4+T cells, macrophages and DCs. UBE2T may play important roles in the cross-talk between tumor and immune environment in order to drive tumorigenesis.

3.5 UBE2T Is Correlated with Typical Immune Marker Genes in LUAD and STAD

We used the TIMER database to show the relationships between UBE2T and the immunological marker sets of diverse immune cells from LUAD and STAD. These immune cells include CD8+ T cells, T cells (general), B cells, monocytes, tumor associated macrophages (TAMs), neutrophils, natural killer (NK) cells, and DCs, which contribute to the immunosuppressive or immunomodulatory features of the tumor microenvironment. CD4 T cells may develop into a variety of helper and regulatory T-cell lineages, including Th1, Th2, Th9, Th17, TFH, and CD4+Foxp3+ Tregs. In this work, we looked at several types of functional T cells, such as Th1 cells, Th2 cells, and Tregs. We discovered that STAT6 expression levels in T cells had a somewhat unfavorable connection with UBE2T expression in LUAD. Furthermore, a somewhat favorable connection between UBE2T and GZMB of T cell fatigue was discovered.

3.6 Correlations between UBE2T and Immune Marker Genes in THYM

In THYM, the correlations between UBE2T and immune marker sets of T cells are complex. There existed strong positive correlations between UBE2T and the expression levels of CD8A (P=1.37e-18, r=0.815) and CD8B (P=5.49e-26, r=0.782) of CD8+T cells, CD2 (P=4.04e-26, r=0.793), CD3D (P=8.44e-20, r=0.722) and CD3E (P=1.06e-30, r=0.832) of T cell (general), GATA3 (P=3.15e-21, r=0.74) of Th2 cells, PD-L1 (PDCD1) (P=1.79e-15, r=0.656) of T cell exhaustion in THYM. However, significant negative correlations were identified between UBE2T and the expression levels of STAT4

(P=2.26e-4, r=-0.337), TNF (P=4.38e-9, r=-0.514) and TNF-α (IFNG) (P=5.28e-7, r=-0.448) of Th1 cells, STAT5A (P=9.16e-5, r=-0.357) and STAT6 (P=7.63e-4, r=-0.31) of Th2 cells, STAT3 (P=1.11e-5, r=-0.397) of Th17 cells, FOXP3 (P=6.17e-6, r=-0.408) of Tregs, CTLA4 (P=5.51e-6, r=-0.409) of T cell exhaustion in THYM.

4 CONCLUSIONS

Lung cancer is widely recognized as one of the most common malignant tumors and the main cause of cancer-related mortality worldwide. Similarly, breast cancer still has the highest fatality rate among gynecological cancers due to widespread intraperitoneal metastases at an early stage and a lack of effective early detection measures. Despite the fact that immunotherapy has been shown to be effective in the treatment of advanced malignancies, cancer immunotherapy has a number of adverse effects as well as other drawbacks. Therefore, there is an urgent requirement for the identification of new targets for immunotherapy for these cancers.

One of the most ubiquitous regulatory processes in all eukaryotes is protein modification via covalent attachment of ubiquitin (Dermani 2019). Ubiquitin and ubiquitin-like proteins modify proteins, which is a fundamental regulatory step in the innate and adaptive immune responses. UBE2T was discovered to be a critical regulator and oncogene in numerous malignancies, including breast, lung, prostate, and bladder cancer, as a member of the ubiquitin-conjugating E2 family in the ubiquitin-proteasome system.Many immune signaling pathways depend on ubiquitin chain production, and the ubiquitin conjugating enzyme is important in immune receptor signaling (Dermani 2019). On the other hand, the relationship between UBE2T expression and immune infiltration levels, on the other hand, has never been detected before. This study initially looked at the levels of UBE2T expression in distinct cancer types using publicly available information. The majority of cancer types, including thymoma, breast, lung, gastric, and ovarian cancer, have elevated UBE2T expression. Following that, we investigated the correlations between UBE2T expression and clinical indications. We discovered that elevated UBE2T expression was associated with a poor outcome in breast and lung cancer. The outcomes for gastric cancer, thymoma, and ovarian cancer, on the other hand, were diametrically opposed. Patients with greater levels of UBE2T expression had a better prognosis. Furthermore, the expression of UBE2T has been linked to the prognosis of individuals with lymph node metastases in breast, lung, and gastric cancer. Further research revealed that high UBE2T levels were, to some extent, associated with tumor purity in LUAD and STAD. The interplay of tumor stroma and tumor-infiltrating lymphocytes has a significant impact on cancer patient outcomes. In LUAD and STAD, we also discovered negative relationships between the degree of UBE2T expression and the infiltration of CD4+ T cells, DCs, and macrophages. THYM, on the other hand, revealed strikingly positive relationships. This implies that UBE2T in LUAD may have immunoregulatory and cancer-promoting characteristics. While STAD and THYM may have sophisticated mechanisms for anticancer activity, It should be mentioned that the link between UBE2T expression and the prognosis of gastric cancer patients contradicted prior research findings. The inconsistent results may be due to differences in the techniques used or differences in the tumor samples examined. Thus, further study is needed to validate our findings and hypothesis.

Based on the findings, we hypothesized that UBE2T may have a role in tumor immunology regulation. So we went a step further and used the TIMER database to find a link between UBE2T expression and immune cell marker genes in LUAD, STAD, and THYM. T cells are exceedingly complicated and diverse in vivo, with continual renewal. We initially looked for links between UBE2T and T-cell marker genes. THYM discovered strong positive connections between UBE2T and CD8A and CD8B of CD8+ T cells, as well as CD2, CD3D, and CD3E of general T cells. This suggests that increased UBE2T expression may be linked to the recruitment of CD8+ T cells and general T cells in THYM. GATA3, a zinc-finger transcription factor in the GATA family, is recognized to be a critical regulator of Th2 development. In THYM, we discovered a substantial positive connection between UBE2T expression and GATA3. These findings suggest that UBE2T may influence Th2 cell development. STAT6 is a downstream effector of Th2 cytokine signaling, and high STAT6 levels indicate a robust T-helper 2 type immunological response (Julia 2017). This study found a substantial negative connection between UBE2T expression and STAT6, indicating that UBE2T is involved in the T-helper type 2 response in LUAD and TYHM. In THYM, there was a strong positive connection between UBE2T expression and PD-L1 (Julia 2017). Furthermore, in LUAD, GZMB is modestly positive correlated with UBE2T expression, but CTLA4 is

strongly negatively correlated with UBE2T expression in THYM. T-cell exhaustion is recognized to contribute to disease development since the immune system's ability to control an infection or tumor decreases as T-cell functioning declines. Our findings suggest that UBE2T may play a role in T cell fatigue in a variety of malignancies. In summary, these findings indicate that UBE2T is involved in T-cell function control and that UBE2T may play a variety of roles in various cancers.

To conclude, UBE2T may play a dual function in several human malignancies, including promoting and preventing carcinogenesis. UBE2T expression is linked to prognosis and immune infiltration levels in CD4+ T cells, CD8+ T cells, neutrophils, macrophages, and DCs from many malignancies, including LUAD, STAD, and THYM. The effects of the UBE2T bidirectional interaction in promoting or inhibiting a tumor phenotype are unknown but should be investigated.

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