A Comprehensive Integrated Analysis of DDX3X Expression, Prognostic Value and Potential Implications for Pan-Cancer Immunity

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Abstract

Background: DEAD-box RNA Helicases (DDX3X) is a category of protein that imitate tumourigenesis, invasion, and immune escape by competing in RNA absorption and binding proteins, but allure system debris is expected purified.

Methods: In our research, Cancer Genome Atlas and the Genotype-Tissue Expression Database were discovered to decide the changed verbalization of DDX3X in pan-carcinoma growth, and TIMER (Tumor Immune Estimation Resource) was used to discover the verbalization of DDX3X and the level of invulnerable combination. It's rooted that DDX3X verbalization was well compared accompanying an assortment of diseased invulnerable genes, invulnerable container combination and cut, carcinoma mutational load, and DNA microsatellite inconstancy. DDX3X keep thus be secondhand as a prognostically appropriate immunotherapeutic goal for malignancy forecast.

Introduction

Recently, carcinoma has enhanced a demanding warning to mankind's fitness accompanying the occurrence and mortality progressively ascending [1]. Although therapeutic alternatives in the way that surgery, radiotherapy, chemotherapy, immunization, targeted therapy, recombinant vaccines, and additional emerging situation systems are curving more mature [2, 3] the five-year overall survival is still not ideal [4, 5]. Immunotherapy can turn on invulnerable containers shy in the swelling microenvironment [6], by lowering oxidative stress and the hypoxic environment of common containers, that not only reduces death but has defects in the way that depressed response rate and extreme occurrence of adverse events (AEs) [7]. The tumor immunotherapy's response rate is meticulously connected with the tumor microenvironment (TME). The cellular components and non-cellular components in TME can arbitrate the immune evasion of tumor cells and play a key function in the immune reaction [8, 9]. Therefore, contemplating the organic indicators of immune-complementary proteins while multi-scale biological effects all the while the response of TME to immunotherapy can specify new objectives for forecasting the prognostic risk of inmates.

DDX3X is a classification of proteins in TME accompanying critical venture in protein phosphorylation [10], nuclear spots [11], and transcriptional coactivators [12]whatever is associated with a variety of malignant tumors to a degree medulloblastoma [13, 14], prostate malignancy [15], and colorectal malignancy [16]. Targeting DDX3X is further an active process to eradicate malignancy stem cells (CSCs). DDX3X was bearable to advocate malignant cell proliferation [17], phosphorylation, invasion, and metastasis, and advance cellular immune escape by reconstructing the local microenvironment of tumors, which is had connection with cells recruiting supporting-provocative and TME inflammatory cytokines delivering.

In our study, we comprehensively assessed the expression, methylation level, and immune cell infiltration of DDX3X in pan-carcinoma calculated magnetism equivalence with carcinoma prognostic value, and
envisioned its potential immune function detached cancers and appeal potency as a carcinoma-analogous prognostic biomarker and immune mark.

**Materials And Methods**

4.1 DDX3X Expression in Pan-Cancer

The Cancer Genome Atlas (TCGA, https://www.cancer.gov/) database, which is long-established for comprehensive investigations of human malignancy types, was occupied to scrutinize the signature characteristic verbalization of DDX3X across various malignancy types. Our research method follows the logical idea of Chen's published paper which could be found at https://www.frontiersin.org/articles/10.3389/fmolb.2021.789703/full [18], and studies the potential biological value of key factors for bioinformatic analysis, the prognostic value of immunotherapy target correlation and other potential biological value by mining database and R language. RNA sequencing dossier and dispassionate repercussion intelligence for inmates accompanying 33 types of cancers were downloaded from the TCGA database. Because the rational tissues sequencing data contained in the TCGA are very restricted and many inmates lack transcriptome sequencing results for their rational tissues, we gained data for normal tissues from the Genotype-Tissue Expression (GTEx) database. The cell line expression matrix of DDX3X in pan-malignancy was gathered from the CCLE (https://sites.broadinstitute.org/ccle/datasets) dataset. The above evaluations were assembled utilizing the R (v4.0.3) software package ggplot2 (v3.3.3). R software v4.0.3 and ggplot2 (v3.3.3) were secondhand for visualization. R software v4.0.3 was used for statistical analysis.

4.2 DDX3X Expression and its Clinical Correlation in Pan-Cancer

The correlations of DDX3X expression with tumor stage and DNA methylation were investigated using the UALCAN database (http://ualcan.path.uab.edu/).

4.3 cBioPortal Database

The genetic alterations of DDX3X in different cancer types were obtained using the cBioPortal database.

4.4 The Prognostic Potential of DDX3X in Pan-Cancer

The survival data from 33 types of tumors were acquired from the TCGA database for further overall survival (OS), disease-specific survival (DSS), and disease-free interval (DFI). Univariate Cox regression analysis was used to evaluate DDX3X-associated survival accompanying the R package limma, survival, and forest plot to show the p-value, HR, and 95% CI. The Kaplan-Meier (KM) arrangement was used to investigate the prognostic value of DDX3X savage cancers utilizing the R packages limma, survival, and survminer. R software v4.0.3 was secondhand for statistical evaluation.

4.5 Univariate and Multivariate Cox Regression Analyses and Construction of a Nomogram
Cox regression analysis, including univariate, and multivariate analyses, was used to examine the prognostic value of DDX3X in KIRC, LGG. The forest plot was constructed using the R package “forest plot” to exhibit the hazard ratio (HR), 95% CI, and p-value. The nomogram was constructed using the R package “rms”.

4.6 Co-expression analysis.

We evaluated common immune checkpoints and immune marker genes. The co-expression relationship between DDX3X and these genes was calculated using the package. A heat map of DDX3X co-expression with immune checkpoint genes was drawn using the R packages “reshape2” and “R Color Brewer”. All graphics and data analyses were completed on the R platform (3.6.3 version).

4.7 Correlation of DDX3X Expression With Tumor Cell Infiltration and Immune Modulator Genes in Pan-Cancer

We acquired the dossier for 33 types of human malignancy in TCGA from the GDC data portal website. For predictable immune score calculation, we used the R software package “Immueneconv” to desegregate two of together latest algorithms, containing TIMER, and xCell. Heatmaps of the immune infiltration scores or immune modulator genes and DDX3X interpretation apathetic tumor types were engendered accompanying Spearman equating interpretation. The horizontal axis in the heatmaps shows the type of malignancy, the vertical axis shows distinct immune cell infiltration scores, and the color shows the interrelationship coefficients. Furthermore, R software v4.0.3 was used for analytical interpretation.

4.8 Relationships Between DDX3X Expression and TMB or MSI in Pan-Cancer

We acquired the data for 33 types of human malignancy in TCGA from the GDC data portal website. For the pan-malignancy report, the horizontal axis shows the interrelationship interdependent between DDX3X verbalization and TMB/MSI, the ordinate is the type of malignancy, the capacity of the dots in the figure shows the scope of the equivalence coefficient, and the miscellaneous banner shows the significance of the p-value. A correlation study between DDX3X and TMB/MSI was executed utilizing Spearman’s method and R software v4.0.3 was used for demographic evaluation. A p-value inferior to 0.05 was deliberately statistically momentous.

Results

5.1 DDX3X Expression is Disparate in Human Pan-cancer

Based on the results from TCGA data separate, DDX3X expression was heightened in STAD, and CHOL, since deteriorated in LUAD, LUSC, BRCA, KICH, UCEC, KIRP, BLCA, THCA, THYM tissues distinguished accompanying adjacent rational tissues (Figure 1A). Moreover, we, therefore, examined the expression of DDX3X apathetic malignancy cell lines following the CCLE database (Figure 1B). Because various cancers lack analogous normal tissue controls, we connected the data from the TCGA and GTEx.
After combining the data from TCGA and GTEx, the disagreement of DDX3X completed significance in 24 consumed 33 tumor types. DDX3X expression was higher comprehensively in CHOL, ESCA, GBM, GBMLGGT, LGG, PAAD, LAML, and STAD but lower in ACC, BLCA, BRCA, KICH, KIPAN, KIRP, LUAD, LUSC, OV, PRAD, SKCM, TGCT, THCA, UCEC, and UCS (Figure 1C).

5.2 Association of DDX3X Expression With Clinicopathological Features in Different Cancer Types

The connection between DDX3X expression and the clinicopathological characteristics of inmates accompanying various cancers was examined established individual malignancy stages, containing stages 1, 2, 3, and 4. DDX3X expression was universally raised in HNSC, KICH, KIRP, LUSC, and STAD (Figure 2). In contrast, DDX3X expression was severely dropped off in BLCA, BRCA, COAD, THCA, and UCEC. Moreover, DDX3X expression was fixed in a few cancers, containing ESCA, LIHC, KIRC, SKCM, and UVM.

5.3 Prognostic Overall Survival Values of DDX3X in Human Pan-Cancer

Regarding the overall survival (OS) analysis, Cox regression results from 33 types recommended that DDX3X expression was noticeably related to OS in 5 types, containing LAML, LGG, LIHC, KIRC, and SKCM (Figure 3A). The results from the K-M survival curves demonstrated that higher DDX3X expression corresponded with accompanying worse OS in LGG, and LIHC, but with better OS in LAML, KIRC, and SKCM (Figure 3B).

5.4 Prognostic Disease-Specific Survival and Disease-free Interval of DDX3X in Human Pan-Cancer

Moreover, we investigated the DSS and DFI relationship accompanying DDX3X in pan-cancer patients. K-M of DSS analysis indicated that upregulated DDX3X expression harmonized accompanying deficient DSS in victims accompanying KICH, LGG, and PAAD, but accompanying favorable DSS in victims accompanying KIRC, STAD, and OV (Figure 4). K-M of DFI analysis indicated that upregulated DDX3X expression corresponded with accompanying miserable DFI in patients accompanying PCPG, but accompanying favorable DFI in victims accompanying OV and STAD (Figure 4).

5.5 DDX3X is an Independent Prognostic Factor in KIRC and LGG

To further validate whether DDX3X was a liberated prognostic ingredient in cancers, univariate and multivariate Cox regression interpretations were executed to establish miscellaneous clinicopathological characteristics, to a degree age, gender, race, radiation therapy, T stage, N stage, M stage, and TNM stage. Univariate Cox regression evaluation demonstrated that DDX3X expression (p < 0.05), T stage (p < 0.001), N stage (p < 0.001), M stage (p < 0.001), and TNM stage (p < 0.001) were significantly corresponded accompanying OS in KIRC (Figure 5A); DDX3X expression (p < 0.01), age (p < 0.001), grade (p <0.001), and radioactivity-therapy (p < 0.05) were corresponded accompanying OS in LGG (Figure 5D). Multivariate investigation indicated that M stage (p < 0.01) significantly checked to accompany OS in KIRC (Figure 5A); DDX3X expression (p < 0.05), age (p < 0.001), and grade (p <0.01) corresponded accompanying OS in LGG (Figure 5D). In addition, a nomogram was assembled to establish a
multivariate study (Figures 5B, E). The C-index and graduated system curve rooted the veracity in envisioning the 1-, 3-, and 5-year continuation rates. The C-index of the prognostic nomogram was 0.848, and 0.821 in KIRC and LGG, separately accompanying moderate veracity (Figures 5C, F).

5.6 DNA Methylation and Genetic Alteration Analysis of DDX3X in Pan-Cancer

A flourishing corpse of deposition advocates that DNA methylation is an epigenetic microscopic mechanism for deoxyribonucleic acid interpretation whatever DNA hypermethylation leads to the inactivation of a comprehensive range of carcinoma suppressor genes. Therefore, we examined the potential link between DNA methylation and DDX3X expression. Concerning the TCGA database, we commemorated that the DNA methylation level of DDX3X was heightened in KIRC, KIRP, LUSC, and PRAD, but deteriorated in TGCT and UCEC based on the UALCAN database (Figure 6A). Additionally, we examined the amendment repetitiveness of DDX3X apathetic tumor types following the cBioPortal database. The top five occurrence rate of hereditary deviations of DDX3X was commemorated in the abdomen, MBN, melanoma, endometrial, and esophageal. Deep erosion existed as the predominant originator of esophageal, yet, mutations were the originator of the surviving four carcinomas (Figure 6B).

5.7 Association of DDX3X Expression and Immune Cell Infiltration in Pan-Cancer

Because immune-infiltrating cells play an outstanding part in tumor initiation and development, we thus estimated the corporation between DDX3X expression and the infiltration levels of six dominant immune cells in 32 types of cancers. Utilizing the data from the TIMER database, the interrelationship between DDX3X expression and the infiltration levels of these immune cells was investigated individually. The outcomes were tacit that DDX3X expression was noticeably tied in accompanying the infiltrating level of B cells in 16 types of tumor, CD4+ T cells in 18 types of tumors, CD8+ T cells in 18 types of tumors, macrophages in 17 types of tumors, neutrophils in 22 types of malignancy, and myeloid decorated with flowers cells in 17 types of malignancy (Figure 7A). In addition, DDX3X interacted accompanying these six types of immune cells in COAD, KIRC, LIHC, PAAD, PRAD, and READ (Figure 7A). To prove the connection between DDX3X expression and infiltration of 38 immune cell subtypes, we resorted to the xCell database. DDX3X expression was negatively related to the infiltration grades of most immune cells in KIRC, SARC, TGCT, THCA, and UCEC (Figure 7B).

5.8 Relationships Between DDX3X Expression and Immune Checkpoint Genes in Pan-Cancer

Because immune checkpoint genes play a substantial function in carcinoma immunotherapy, the interrelationships between DDX3X and immune checkpoint genes, immune inhibitors, and immunostimulators were subsequently investigated. Conspicuously, we commemorated that DDX3X significantly positively corresponded with most immune checkpoint genes like VEGFB but negatively corresponded with most immune checkpoint genes, containing BTN3A1, BTN3A2, CD274, EDNRB, ENTPD1, HMGB1, TLR4, TNFSF4, VEGFA (Figure 8).

5.9 Relationships Between DDX3X Expression and TMB and MSI in Pan-Cancer
TMB and MSI are two emerging biomarkers accompanying the immunotherapy feedback. The relationships between DDX3X expression level and TMB across miscellaneous malignancy types were still investigated. The expression level of DDX3X was strikingly and positively corresponded to accompanying TMB in abundant cancers, containing LUSC, but negatively correlated with accompanying TMB in LIHC, THCA, and UVM. (Figures 9A, C). Additionally, the correlation of DDX3X expression accompanying MSI was further investigated in pan-tumor, among which DLBC, LIHC, THCA, and UVM exhibited an unfavorable equivalence while CHOL, LUSC, READ, and UCEC exhibited a positive interrelationship accompanying DDX3X expression (Figures 9B, C).

5.10 Correlation Between DDX3X Expression Level and Tumor Microenvironment
The expression of DDX3X may be approximately related to immune escape and the micro-environment. The immune score anticipates the response to carcinoma immunotherapy. Analysis of the connection between DDX3X expression and immune scores affirmed that higher DDX3X expression levels cooperate with higher immune scores and stromal obligation (Figure 10).

Discussion
On account of its high occurrence and mortality, carcinoma has dramatically obstructed humanity's fitness worldwide, accompanying annual morbidity of approximately 3.9% and a mortality rate of 2.5% in the past decade, the malignancy brought about 10 million dying incidents in 2020 [19]. Notwithstanding that the diagnosis and characteristics of the growth of advanced victims are unsatisfactory, early detection and prompt medication can effectively improve the prognostication and survival for inmates [20, 21]. The ordinary therapy methods for malignant tumors currently contain surgery, radiotherapy, chemotherapy, immunization, targeting, recombinant vaccines, etc., but their efficiency is not unattainable [22]. Therefore, it is extraordinarily indispensable to survey biomarkers and microscopic pathways related to carcinoma pathogenesis and management to determine matching guidance for the early detection of cancerous disease and treatment strategies. DDX3X is a category of proteins in TME accompanying superior endeavor in protein phosphorylation, nuclear spots, and transcriptional coactivators, mainly related to DNA transcription, and its abnormal expression will cause chromosomes to approach misfolded or even rearranged during transcription, generating rational deoxyribonucleic acid mutations and oncogene activating [23] and inhibited of platinum resistance in ovarian cancers via IncRNA RMRP/DDX3X/PHGDH [24]. DDX3X is contributing to a variety of malignant tumors to a degree of lung malignancy [25], prostate malignancy [26, 27], breast malignancy [28], and colorectal malignancy [29], whatever is related to DDX3X recruiting supporting-inflammation cells and leaking TME inflammatory cytokines to advance carcinoma development. DDX3X is likewise a persuasive resource to eradicate malignancy stem cells (CSCs) [12], DDX3X overexpression induces ERα phosphorylation in breast epithelial cells [30]; DDX3X advocates the G1/S cycle conversion of medulloblastoma cells and induces oral squamous cells by combining accompanying unusual activating of ATK/mTOR pathway by KRT17, all of that generates the malignant proliferation of normal cells [31], DDX3X can also embark on the RNA metabolic modification process [32], bind to proteins to promote distant carcinoma metastasis, and
evade immune attack. DDX3X will bind to Casein Kinase lisoformepsilon (CK1ε) to cause Wnt/β-catenin signaling pathway activation [33], culminating in distant metastasis of lung adenocarcinoma (LAD) cells [34], it reverses the translation process of circular RNA (circRNA) in glioblastoma stem cells (GSCs) [35, 36], acknowledging carcinoma tissue to evade immune attack, accordingly, it commits metastasis in diverse tissues; high DDX3 expression via a KRAS/ROS/HIF-1α reaction loop takes care of reinforce CTX subtlety in KRAS-WT colorectal malignancy [37]; DDX3X keep downregulate IFNB1-STAT1 signaling pathway accompanying IncRNARFPL1S-202 to inhibit the chemoresistance and progression of ovarian tumor [38], and high expression levels of DDX3 in head and neck squamous cell carcinoma (HNSCC) correlate with lymph node metastasis and poor prognosis [39]. In this study, utilizing bioinformatics methods, searching the public databases of TCGA, GTEx, UALCAN, and cBioPortal, we comprehensively demonstrated the expression level of DDX3X and appeal immunological connection to numerous malignancy types. We establish that proficiency was an oddly high expression of DDX3X in 33 malignancy types. DDX3X expression level is correlated with the unfavorable prognosis of patients with various types of tumors (OS, DSS, PFI, and DFI). Meanwhile, the expression of DDX3X has closely associated with TMB, MSI, MMR, and DNA methylation [40]. In addition, this study demonstrated that the expression of DDX3X in many tumors (especially ACC, TGCT, and UCEC) negatively correlated with the immune and stromal scores. In pancreatic CSCs, the knockdown of PAF1 reduces the ability of orthotopic pancreatic tumors to develop and progress in mice and their numbers of CSCs, which provides strategies that PAF1-PHF5A-DDX3 complex might be developed to slow or inhibit the progression of pancreatic cancer [41]. In summary, DDX3X may become a biomarker that provides some new ideas for the immunotherapy of tumors [17]. According to previous studies, DNA methylation regulates the promoter GpC island, which is responsible for the regulation of proteins bound to DNA and is involved in the carcinogenesis and development of various malignancies such as ovarian cancer [42]. Our study found that DDX3X was positively associated with DNA methylation in KIRC, KIRP, LUSC, and PAAD, but negatively associated with TGCT and UCEC, according to the UALCAN database. Deep depletion is extensively involved in the internal modification of RNA and plays a key role in RNA metabolism and various biological processes. In acute myelogenous leukemia (AML), major leukemogenic H3K4 methylation can support cooperation specificity within an epigenetic framework [43]. However, little is realized about the association of DDX3X expression with genes associated with profound attrition, and further experiments are required. Our study found that the incidence of DDX3X gene variants was extremely associated with oesophageal cancer. In recent years, research on tumor immunotherapy has intensified, and various immune monoclonal antibodies such as PD-L1 and PD-1 have become high-level recommended drugs in guidelines for lung cancer, breast cancer, and cutaneous melanoma [44]. And our studies have confirmed that DDX3X expression is associated with a variety of ICP genes, especially in cancers such as HNSC, READ, OV, PRAD, and THCA, while DDX3X is closely associated with cellular components of TME, immune cells, and stromal cells, which can influence tumor cell growth and differentiation [17]. Previous studies have shown that activation of tumor-infiltrating immune cells (TIICs) and T cells is closely associated with survival in patients with breast and lung cancer [45, 46]. Therefore, modulating the level of TICs provides a new direction for tumor immunotherapy. Various immune cells may promote or suppress tumor development through different mechanisms. Our study also found that
DDX3X was positively correlated with these six immune cells in COAD, KIRC, LGG, LIHC, PAAD, PRAD, READ, and THCA, but negatively correlated with these immune cells in ACC, ESCA, and GBM. In contrast, in the xCell database, DDX3X expression was negatively correlated with the level of infiltration of most immune cells in KIRC, SARC, TGCT, THCA, and UCEC. This suggests that the higher the expression of DDX3X, the lower the number of immune cells and stromal cells in TME. DDX3X may inhibit or promote cancer progression by aggregating and regulating immune infiltrating cells. In gastric and colorectal cancers, high macrophage infiltration is associated with poor prognosis [47]. Therefore, studying the relationship between DDX3X and immune infiltrate-associated cells for different tumors could facilitate tumor immunity and drug development therapy. Our study found that DDX3X expression was significantly associated with infiltration levels of B cells in 16 cancers, CD4+ T cells in 18 cancers, CD8+ T cells in 18 cancers, macrophages in 17 cancers, neutrophils in 22 cancers, and bone marrow dendritic cells in 17 cancers (Figure 7A). In addition, DDX3X was positively correlated with these six types of immune cells in COAD, KIRC, LIHC, PAAD, PRAD, and READ (Figure 7A). DDX3X expression was negatively correlated with the level of infiltration of most immune cells in KIRC, SARC, TGCT, THCA, and UCEC. Therefore, depending on the immune infiltration of different tumors, it is possible to develop corresponding immunotherapy, anti-tumour treatment is very important.

However, there are still deficiencies in our analysis, containing (a) targeting DDX3X may be a hopeful strategy for Cancer-individual immunotherapy, but before the expected time, there are no limited molecule medications, microarray vectors, and additional accurate therapeutic approaches particularly targeting DDX3X, and we desire to expand technologies such as small molecule drugs, microarray vectors and RNAi for immune cell infiltration of DDX3X in the tumor microenvironment for efficiency authorization. (b) Data excavating in different publicly available databases accompanying miscellaneous data origins will generate a few conflicting conclusions, and in vitro and in vivo experiments additionally, a clinical collection of specimens is needed to cross-validate the relevance of DDX3X to the relevant signaling pathways, immune checkpoint genes, immune cells, etc. attained from the study. (c) Precision immunotherapy such as Cancer vaccines targeting DDX3X demands fundamental and clinical authorization before the final clinical petition and requires a certain amount of sampling size for verification.

**Abbreviations**

Tabel1. Terms and abbreviation
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACC</td>
<td>Adrenocortical carcinoma</td>
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<tr>
<td>BLCA</td>
<td>Bladder Urothelial Carcinoma</td>
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<tr>
<td>BRCA</td>
<td>Breast invasive carcinoma</td>
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<tr>
<td>CCLE</td>
<td>Cancer Cell Line Encyclopedia</td>
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<tr>
<td>CESC</td>
<td>Cervical squamous cell carcinoma and endocervical adenocarcinoma</td>
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<tr>
<td>CHOL</td>
<td>Cholangio carcinoma</td>
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<tr>
<td>circRNA</td>
<td>circular RNA</td>
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<tr>
<td>CK1ε</td>
<td>caseinkinaseIsoformepisilon</td>
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<td>COAD</td>
<td>Colon adenocarcinoma</td>
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<tr>
<td>CSCs</td>
<td>cancer stem cells</td>
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<td>DDX3X</td>
<td>DEAD-box RNA helicase</td>
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<td>DFI</td>
<td>disease-free interval</td>
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<tr>
<td>DLBC</td>
<td>Lymphoid Neoplasm Diffuse Large B-cell Lymphoma</td>
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<td>DSS</td>
<td>disease-specific survival</td>
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<td>ESCA</td>
<td>Esophageal carcinoma</td>
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<td>GBM</td>
<td>Glioblastoma multiforme</td>
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<td>Genotype-Tissue Expression</td>
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<td>GSCs</td>
<td>glioblastoma stem cells</td>
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<td>GSEA</td>
<td>Gene Set Enrichment Analysis</td>
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<td>HNSC</td>
<td>Head and Neck squamous cell carcinoma</td>
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<td>HR</td>
<td>hazard ratio</td>
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<td>KEGG</td>
<td>Kyoto Encyclopedia of Genes and Genomes</td>
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<td>KICH</td>
<td>Kidney Chromophobe</td>
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<td>LAML</td>
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<td>LIHC</td>
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<td>Lung squamous cell carcinoma</td>
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<td>MESO</td>
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<td>MSI</td>
<td>microsatellite instability</td>
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<td>OS</td>
<td>overall survival</td>
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<td>OV</td>
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<td>Sarcoma</td>
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<td>Skin Cutaneous Melanoma</td>
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<td>STAD</td>
<td>Stomach adenocarcinoma</td>
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<td>TCGA</td>
<td>The Cancer Genome Atlas</td>
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<td>TGCT</td>
<td>Testicular Germ Cell Tumors</td>
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<td>Thyroid carcinoma</td>
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<td>THYM</td>
<td>Thymoma</td>
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<td>TIMER</td>
<td>Tumor Immune Estimation Resource</td>
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<td>TMB</td>
<td>tumor mutational burden</td>
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<td>TME</td>
<td>Tumor Micro-environment</td>
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<tr>
<td>UCEC</td>
<td>Uterine Corpus Endometrial Carcinoma</td>
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<td>UCS</td>
<td>Uterine Carinosarcoma</td>
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<tr>
<td>UVM</td>
<td>Uveal Melanoma</td>
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**Declarations**

**DATA AVAILABILITY STATEMENT:** The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author, Huimin Jin (E-mail: HuiminJin@zcmu.edu.cn).

**Declarations:** Not applicable for this article.
AUTHOR CONTRIBUTIONS: Study concept and design: JHM and RSM. Acquisition of data: PX, JJM, and CXY. Analysis and interpretation of data: JHM, PX, and JJM. Statistical analysis: JHM, PX, and CXY. Critical revision and final approval of the article: RSM, and JHM. Study supervision: JHM. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References


Figures
**Figure 1**

**DDX3X Expression is Disparate cruel Pan-malignancy**  
(A) Upregulated or downregulated verbalization of DDX3X in pan-tumor from TCGA datasets. (B) The mRNA level of DDX3X in miscellaneous human tumor cells following the CCLE database. (C) DDX3X characteristic verbalization across diversified tumor types in the TCGA and GTEx databases. *p < 0.05; **p < 0.01; ***p < 0.001.
**Figure 2**

**Correlation of DDX3X expression and clinicopathological parameters across different cancer types.** The clinical equivalences between DDX3X expression levels and carcinoma stage aloof malignancy types were checked utilizing the UALCANCN database. *p < 0.05; **p < 0.01; ***p < 0.001.
Figure 3

Prognostic Overall Survival Potential of DDX3X in Pan-cancer. (A) Correlation investigation of DDX3X expression accompanying OS by the Cox regression model in miscellaneous cancers. (B) Using Kaplan-Meier methodology, OS curves equating high and low expression of DDX3X in numerous tumor types.
Figure 4

Prognostic Disease-specific Survival and Disease-free Interval Potential of DDX3X in Seven Different Types of Cancers. (A-G) DSS and DFI curves contrasting high and low expression of DDX3X in OV, PCCP, STAD, PAAD, KIRC, KICH, and LGG utilizing Kaplan-Meier methodology.
Figure 5

Internal Validation of DDX3X as an Independent Prognostic Factor for KIRC Patients and LGG Patients.

(A, D) Univariate and multivariate Cox regression analyses were executed to determine DDX3X as a separate prognostic element. (B, E) A prognostic nomogram coordinating DDX3X expression and clinicopathologic variables was assembled to estimate OS. (C, F) Calibration plots to forecast the OS of KIRP and ACC at 1, 3, and 5 years.
Figure 6

**DNA Methylation and Mutation Profile of DDX3X in Pan-cancer.** (A) The promoter methylation level of DDX3X across divergent malignancy types was examined following the UALCAN database. (B) The transformation repetitiveness of DDX3X accompanying diverse mutation samples was acquired from the cBioPortal database. *p < 0.05; **p < 0.01; ***p < 0.001.
Figure 7

**Correlations of DDX3X Expression with the Infiltration Level of Immune Cells Across Different Cancer Types.** (A) Heatmap of interrelationships between the expression of DDX3X and the level of immune infiltration in 33 types of human tumor utilizing TIMER. (B) Heatmap of interrelationships between the expression of DDX3X and the level of immune infiltration in 38 types of human tumor utilizing xCell. *p < 0.05; **p < 0.01; ***p < 0.001.
Figure 8

Correlations of DDX3X Expression with Immune Checkpoint Genes Across Different Cancer Types. *p < 0.05
Figure 9

**Correlations of DDX3X Expression and TMB and MSI in Pan-cancer.** (A) The stick chart shows the associations between DDX3X expression and TMB in pan-cancer. (B) The stick chart shows the associations between DDX3X expression and MSI in pan-cancer. (C) Relationship between DDX3X expression and MSI in 4 tumor types, the relationship between DDX3X expression and TMB in another 4 tumor types. Correlation analysis was performed using Spearman’s method.
Figure 10

Correlation Between DDX3X, Immune Score, Stromal Score, and Estimate the Score of TCGA Dataset by R in 7 Types of Cancer. (A) correlation between DDX3X and Stromal-Score in COAD, KIPAN, and PAAD. (B) The interrelationship between DDX3X and immune scores in DLBC, TGCT, and UCEC. (C) correlation between DDX3X and estimate score in ACC, PAAD, and TGCT.