A Potential Prognosis and Immune Biomarker in Cancer: DICER1

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Abstract

Background: DICER1 plays a significantly important role in short dsRNA-mediated post-transcriptional gene silencing that is deeply embedded in the network of cancer genes. Aberrant expression and mutation of DICER1 have been studied and reported to be closely associated with tumorigenesis and development, while lower levels of DICER1 mRNA or protein are associated with poorer prognosis in some cancers. However, there is little research about the effect and mechanism of mutated DICER1.

Materials and Methods: In our study, DICER1 mutation in the TCGA database from the top 10 cancers were analyzed to explore the effect of DICER1 mutants in cancer prognosis and the possible potential mechanisms.

Results: We found that DICER1 mutation was closely related to better clinical outcomes in pan-cancer and uterine corpus endometrial carcinoma (UCEC) treatment, which meant that DICER1 could be served as a prognosis factor for pan-cancer, especially UCEC. And mechanism research indicated that DICER1-mut facilitated antitumor immunity, which could be the potential mechanism for DICER1-mut prognosis value. Moreover, tumor microenvironment (TME) features and higher TMB of DICER1-mut manifested that DICER1 may be a potential biomarker of immunotherapy, which needed more clinical and basic research to validate.

Conclusions: In summary, our finding suggested that DICER1 may be a potential prognostic biomarker and was associated with TME in UCEC. In addition, it might be a marker of immunotherapy.

Introduction

DICER1 encodes a double-stranded RNA (dsRNA) endoribonuclease, which is required by the RNA interference (RNAi) and small temporal RNA (stRNA) pathways to produce short interfering RNAs (siRNA) and mature microRNAs.¹⁻⁶ Germline mutation in DICER1 was associated with a variety of benign and malignant tumors, which also named DICER1 syndrome, including pleuropulmonary blastoma (PPB), cystic nephroma (CN), Sertoli-Leydig cell tumor (SLCT), multinodular goiter (MNG), thyroid cancer, rhabdomyosarcoma, and pineoblastoma. Recently, DICER1 somatic mutations are reported in several cancer types (lung, colorectal, pituitary, thyroid, ovarian, parathyroid, pineal gland, endocrine pancreas, adrenocortical, paraganglioma, medullary, and testicular tumors).⁷⁻⁸ Recurrent somatic mutations were detected in metal-binding residues within the RNase IIIb domain of DICER1, which decreased the expression of some tumor-suppressive miRNAs. Impaired DICER1 function was also reported to promote tumorigenesis, stemness, and metastasis in cancer cells.⁹⁻¹⁰ In addition, abnormal DICER1 expression exists in multiple cancer types and is associated with poor prognosis. It has been shown that lower DICER1 levels are associated with poorer prognosis in melanoma, colorectal, endometrial, and ovarian cancer.¹¹⁻¹⁶ However, the role of DICER1 mutants in tumor prognosis remains unclear. In our research, DICER1 mutation in The Cancer Genome Atlas (TCGA) database from the top 10 cancers were analyzed to explore the effect of DICER1 mutants in cancer prognosis and the possible potential mechanisms.

Materials And Methods

Data collection and Statistical Analysis

10953 NGS of clinical data and 4740 RNA-seq data were collected from TCGA database (www.cbioportal.org),¹⁷ and survival information was collected from 1661 pan-cancer patients in MSKCC cohort.¹⁸ The Kaplan–Meier (K–M) survival curves were generated to demonstrate the mutated group's overall survival (OS) and wild-type patients. Univariate and multivariate analyses of survival were conducted for both the mutation signature and clinicopathologic factors. The R package called “survival” was utilized to perform the survival analysis. Clinical categorical data were tested using the chi-square test and the chi-square test for trends. For continuous variables, statistical significances were evaluated with the Student's t-test.

Bioinformatics

TMB is a measure of the total number of mutations per megabyte of tumor tissue, we calculated the TMB for each sample is equal to the total mutation frequency/45, which is routinely taken based on the length of the human exon. TMB per megabase is calculated by the size of the coding region of the target. The absolute quantities of individual immune cell subtypes were inferred from the TPM expression data by using the CIBERSORT program¹⁹, which can accurately quantify the percentage of various tumor-infiltrating immune cells (TIICs) under the complex “gene signature matrix” based on 547 genes¹⁹. Estimate-, Immune- and Stromal scores of tumor samples were calculated with the ESTIMATE algorithm of the “estimate” package.²⁰ This algorithm is composed of a nonimmune stromal score parameter and an immune score parameter. In our work, we refer to ImmuneScore as the immune score subcomponent of the ESTIMATE algorithm, which infers the degree of immune cell infiltration within tumor tissue based on the expression data of 141 immune-related genes previously shown to correlate with the presence of leukocytes.²¹ The activity of cytotoxic T cells within each sample was estimated utilizing the CYT score, which was calculated through the transcript levels of two key cytolytic effectors, granzyme A (GZMA) and perforin (PRF1).²⁰ Total TILs score was calculated as the average of all cell scores whose correlation with PTRPC (CD45) exceeded 0.6, which was used to measure the abundance or depletion of each cell population relative to total TILs.²² IFN- γ is a key cytokine produced by activated T cells, as well as natural killer (NK) and NK T cells in the tumor microenvironment, and it plays an important role in coordinating this process²³ and we use 10-gene “preliminary IFN- γ ” signature (IFNG, STAT1, CCR5, CXCL9, CXCL10, CXCL11, IDO1, PRF1, GZMA, and MHCII HLA-DRA) to calculate the IFN- γ score.²⁴ Heatmaps of gene expression data with corresponding clinicopathologic characteristics were created with the R package ComplexHeatmap.²⁵ ssGSEAs were performed using the R software package GSVA.²⁶ We utilized the “DEseq2” R package to extract the DEGs by applying the criteria $p\text{-value} < 0.01$ and $|\log_2\text{FC}| \geq 1$. To investigate potential biological processes (BP), cellular components (CC), molecular functions (MF), and signaling pathways related to DEGs, we used representation analysis, and applied Gene Ontology (GO) and Kyoto encyclopedia of genes and genomes (KEGG) pathway analyses by clusterProfiler package in R, with the cutoff value of $\text{FDR} < 0.01$.²⁷

Results

DICER1 Mutations in TCGA datasets

The mutation landscape of DICER1 was determined in the top 10 cancer types from the TCGA database. In total, 2.91% (319/10953) patients with TCGA harbored DICER1 mutation. The top 10 cancer types in TCGA included uterine corpus endometrial carcinoma (UCEC) (DICER1 mutation rate, 12.6%, 67/530), skin cutaneous melanoma (SKCM) (7.2%, 34/467), colon adenocarcinoma (COAD) (5%, 20/399), lung squamous cell carcinoma (LUSC) (3.5%, 17/492), bladder cancer (BLCA) (3.4%, 14/412), cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC) (3.1%, 9/289), lung adenocarcinoma (LUAD) (2.3%, 13/567), stomach adenocarcinoma (STAD) (2.2%, 10/437), head and neck squamous cell carcinoma (HNSC) (2.1%, 11/508), breast cancer (BRCA) (1.1%, 11/986). The unfolded DICER1 protein structure was shown in Fig. 1, indicating the approximate position of 280 somatic DICER1 substitution mutations from the top 10 cancers in TCGA. Four hotspot mutations (p.R944, p.S1344, p.E1705, p.D1810) were identified, of which three are located in the functional domain of DICER1, RNase III domain (Fig. 1).

DICER1-mut predicts better prognosis in pan-cancer and UCEC

We assessed the association between DICER1 and clinical characteristics of pan-cancer and each cancer obtained from TCGA datasets. In the pan-cancer cohort, which comprises ten types of tumors, we found that the DICER1-mutant (DICER1-mut) group showed a more satisfactory overall survival outcome than the DICER1-wild (DICER1-wt) group, based on results of the log-rank test and Kaplan-Meier analysis (Fig. 2A). Furthermore, we observed a significant association between DICER1-mut and longer overall survival (OS) in UCEC (Fig. 2B), while no significant difference in OS was found in other types of tumors (Figure S1). Moreover, COX proportional hazard model analysis showed DICER1-mut positively correlated with better overall survival (OS) in UCEC ($p = 0.004$), while no association was observed in other cancer types (Fig. 2C). Notably, a consistent trend was discovered in SKCM, COAD, BLCA, and STAD, but there was no statistical significance. One may concern may be that the DICER1 mutation frequency is relatively low in tumors except for UCEC. These results showed that DICER1-mut was more likely to be a positive prognosis biomarker in pan-cancer and UCEC.

Potential mechanisms in predicting prognosis in pan-cancer and UCEC

To further explore the fundamental mechanism of the prognosis values of DICER1 mutations, we performed a tumor microenvironment (TME) analysis of pan-cancer and UCEC. CIBERSORT analysis of the RNA-seq data from the top 10 types of cancers in the TCGA dataset showed that CD8 + T cells, activated CD4 memory T cells, follicular helper T cells, activated NK cells were more abundant in DICER1-mut tumors, conversely, DICER1-mut was negatively correlated with the naïve B cells, resting CD4 memory T cells, resting dendritic cells and resting mast cells (Fig. 3). We further investigated the effect of DICER1 mutations on TME in UCEC, which showed that DICER1 mutation exerted a significant influence in UCEC TME, which was higher levels of infiltrating activated CD4 + memory T cells, follicular helper T cells, Eosinophils, while a lower level of Treg cells (Fig. 4A). Next, we evaluated the association between

DICER1 mutations and immune signatures. As shown in Fig. 4B-E, The DICER1-mut group in UCEC had significantly higher levels of cytotoxic T lymphocytes (CTL score), cytolytic activity (CYT score), total TILs score, and cytokine expression than DICER1-wt. These results suggested that DICER1-mut facilitated antitumor immunity, which could be the potential mechanism for DICER1-mut prognosis value. Based on this, we evaluated the expression of immune checkpoint genes to explore the possible impact on immunotherapy and found that the expression of inhibitory checkpoint molecules in UCEC, such as CTLA4 and PDL1 (CD274), was higher in the DICER1-mut group than DICER1-wt group (Fig. 4F), which means DICER1 may be a potential biomarker of immunotherapy.

DICER1-mut patients have higher TMB

To figure out whether DICER1-mut was associated with immunotherapy, we further examined the relationship between DICER1 mutations and tumor mutation burden (TMB), which was considered a common marker of pan-cancer immunotherapy. The results demonstrated that, in 7 types of tumors, including COAD, HNSC, LUAD, LUSC, SKCM, STAD, and UCEC, DICER1 mutation was significantly related to higher TMB ($p < 0.05$) (Fig. 5), especially in COAD, SKCM and UCEC ($p < 0.001$).

DICER1-mut predicts favorable clinical outcomes in an immunotherapy cohort

Given the above, we think DICER1 may be a potential biomarker of immunotherapy. To test the idea, we explored the relationship between DICER1-mut and immunotherapy in MSKCC pan-cancer cohorts. The result showed that the OS of the DICER1-mut group was significantly longer than the DICER1-wt group ($p = 0.0089$) (Fig. 6). Next, tumors with high DICER1 mutation frequency in MSKCC were analyzed, respectively, including melanoma (7.5%, 24/320), colorectal cancer (11.82%, 13/110), non-small-cell lung cancer (2%, 7/350), and bladder cancer (2.79%, 6/215) and however, no significant correlation was found (Figure S2), of which the reason may be too few DICER1-mut samples in the single cancer type.

Discussion

DICER1, a highly conserved endoribonuclease, plays a central role in short dsRNA-mediated post-transcriptional gene silencing that is profoundly embedded in cancer gene networks.²⁸ Aberrant expression of DICER1 has been reported to be closely associated with tumorigenesis and development, while lower levels of DICER1 mRNA or protein have been connected with a worse outcome in lung, breast, skin, and ovarian cancer.^{29–33} Except for the studies focusing on DICER1 expression, the role of mutated DICER1 in cancer received increasing attention. As reported in literatures^{34–40} mutations in DICER1 are recurrent in diverse cancers, which impede miRNA biogenesis and activity leading to tumorigenesis.³⁸ However, there is little research about the effect and mechanism of mutated DICER1. In our research, DICER1 mutations in TCGA data sets from the top 10 cancers were analyzed to explore the impact of DICER1 mutations in cancer prognosis and the possible potential on immunotherapy biomarkers.

In the top 10 DICER1-mut cancers, 2.91% (319/10953) patients harbored DICER1 mutation, of which UCEC had the highest DICER1 mutation frequency, 12.6%. In the other cancers, DICER1 mutants ranged

between 7.2% and 1.1%. 280 somatic DICER1 substitution mutations were called and four hotspots were identified in pan-cancer, which have been reported previously.⁷

Our Kaplan-Meier survival analysis using TCGA data demonstrated that DICER1-mut patients have significantly longer OS than DICER1-wt in the top 10 cancers, which means that DICER1 may be a prognosis factor in pan-cancer treatment. Subsequently, we explored the prognosis effect of DICER1 in each cancer separately. A similar result was observed in UCEC with the highest DICER1 mutation frequency. Previous studies have confirmed the association of lower DICER1 expression and worse DFS, but no significant association with OS of endometrioid endometrial adenocarcinoma.⁴¹ Therefore, we conjectured that DICER1-mut influenced the tumor prognosis not via regulating DICER1 expression but other mechanisms, such as tumor microenvironment. In the other cancers, no significant difference in overall survival (OS) was unfortunately found between DICER1-mut and DICER1-wt, the reason of which may be thought to be too low DICER1 mutation frequency and not enough patients to be analyzed.

To further explore the mechanism, the relationship between TME and DICER1, in consideration of some reports indicating that TME has a vital role in tumor occurrence and development^{42,43}, was analyzed. As expected, according to CIBERSORT results, there were positive correlations between DICER1-mut expression and CD8 + T cells, activated CD4 memory T cells, follicular helper T cells, and activated NK in all 10 cancers, which presented enhanced antitumor immunity in DICER1-mut tumors. Given that DICER1 was also a significant prognosis factor in UCEC, except for CIBERSORT results similar to pan-cancer, another analysis was also performed including immune scores (CTL, CYT, and TILs scores) and cytokine levels. The results in UCEC showed that DICER1-mut was related to antitumor immunity. All above may explain the reason that DICER1 was a prognosis factor of pan-cancer and UCEC. Interestingly, we found that in UCEC the expression of CTLA4 and PDL1 was higher in the DICER1-mut group. As we know, TME features serve as markers for evaluating tumor cell responses to immunotherapy and influence clinical outcomes.⁴² Moreover, in our study TMB, which has been considered an important biomarker for immunotherapy in many types of cancer,⁴⁴ was significantly higher in DICER1-mut tumors. We believed that DICER1 may be a potential biomarker of immunotherapy. To figure out the impact of DICER1 on immunotherapy, we analyzed the association between DICER1-mut and the efficacy of immunotherapy in the MSKCC cohort and found that DICER1-mut could predict favorable clinical outcomes for immunotherapy in pan-cancer. These results indicated DICER1 may be a potential immunotherapy treatment biomarker in pan-cancer, although more clinical data are needed for validation in the single cancer type. However, this retrospective analysis also has several limitations. First, due to the restricted DICER1-mut patients with tumors other than UCEC in our study, the prognosis of DICER1 in other cancers needed to be further explored in the large sample patients. Second, although DICER1 was guessed to be a potential biomarker of immunotherapy, clinical and basic research are required for validation.

Conclusions

In conclusion, our study manifested a favorable link between DICER1 mutation and better clinical outcomes in pan-cancer treatment. Therefore, DICER1 could be served as a prognosis factor for pan-cancer, especially UCEC. To our best knowledge, this study is the first to propose the prognosis of DICER1 in pan-cancer and UCEC. Furthermore, exploration of DICER1 in other tumors and predictive value in immunotherapy are needed in the further.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analysed during the current study are available in the TCGA repository, www.cbioportal.org.

Competing interests

Xia You, Qianru He, Tingting Sun, and Chuang Qi are from Jiangsu Simcere Diagnostics Co., Ltd. The other authors have no conflicts of interest to declare.

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Author contributions

Conception and design: Lewen Bao, Yongpeng Wang. Administrative support: Yongpeng Wang. Provision of study materials: Lifeng Li, Jie Zhao. Collection and assembly of data: Xia You, Qianru He. Data analysis and interpretation: Minghui Ge, Tingting Sun, Chuang Qi. Final approval of manuscript: All authors.

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Figures

Figure 1

A schematic of DICER1 domains with mutations identified from TCGA TOP10 cancers DNA-sequencing datasets.

Figure 2

The relationship between DICER1-mut and OS in pan-cancer and UCEC. (A) Kaplan-Meier survival curves of OS comparing the DICER1-mut group and DICER1-wt group in pan-cancer from TCGA datasets ($p=0.00021$). (B) Kaplan-Meier survival curves of OS comparing the DICER1-mut group and DICER1-wt group in UCEC. ($p=0.027$). (C) Forest plot of association between DICER1-mut and OS in TCGA pan-cancer cohorts. (BRCA patients were excluded because the survival state of them was all alive)

Figure 3

DICER1-mut was associated with enhanced anti-tumor immunity in pan-cancer. The ordinate log10 value represents log10 (cibersort score+1). * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

A

B

C

D

E

F

Figure 4

DICER1-mut was associated with enhanced anti-tumor immunity in UCEC. (A) Comparison of immune infiltration between DICER1-mut and DICER1-wt tumors in UCEC by CIBERSORT. The ordinate log10 value represents log10(cibersort score+1). (B) Comparison of CTL scores (C) CYT scores (D) TILs scores (E) cytokines expression (F) immune checkpoint inhibitor genes expression between DICER1-mut and DICER1-wt tumors in UCEC. * P < 0.05, ** P < 0.01, *** P < 0.001

Figure 5

Association between DICER1 mutations and TMB. DICER1-mut group in COAD, HNSC, LUAD, LUSC, SKCM, STAD and UCEC has significantly higher TMB than DICER1-wt (Mann-Whitney U test, $P < 0.05$). * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Figure 6

DICER1-mut predicted improved clinical outcomes in immunotherapy. Kaplan-Meier curves of OS between DICER1-mut and DICER-wt in the MSKCC-IMPACT cohort.

Supplementary Files

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