TP53 signature score predicts prognosis and immune response in triple-negative breast cancer

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Abstract

Purpose

Triple-negative breast cancer (TNBC) is considered a heterogeneous population and achieving a pathological complete response (pCR) to neoadjuvant chemotherapy (NAC) is an only prognostic factor. Previously, the *TP53* signature (*TP53sig*)-score, an expression profile of 33 genes, is reportedly predictive of the prognosis of all types of early-stage breast cancer. Herein, we analyzed whether the *TP53sig-score* can be subclassified in detail with only a TNBC cohort and investigated the molecular biological characteristics of the higher *TP53sig-score*.

Methods

Publicly available data from TCGA(RNA-sequence) and METABRIC (microarray) and real clinical specimens' s expression data (NanoString Technologies) were used to explore the prognosis and molecular features of TNBC.

Results

The high *TP53sig-score* group in the present study and the cohort in METABRIC tended to have a worse prognosis than the low *TP53sig-score* group ($p=0.583$ and 0.196 , respectively). In both the pCR and non-pCR groups, the high *TP53sig-score* patients tended to have a poor prognosis ($p=0.0739$). Moreover, when the NAC response and *TP53sig-score* were combined, the five-year breast cancer-free rate among the four groups differed significantly ($p=0.043$). In addition, high *TP53sig-score* was related to gene ontology terms, such as "cell differentiation" and "innate immune response. Notably, this group had the potential to respond favorably to immunotherapy according to the tumor immune dysfunction and exclusion model.

Conclusion

Combining the response to NAC and the *TP53sig-score* in triple-negative breast cancer was able to predict an unfavorable prognosis. Further, patients with a high *TP53sig-score* showed a favorable feature associated with immunotherapy

Introduction

Triple-negative breast cancer (TNBC), characterized by estrogen receptor (ER)-negativity, progesterone receptor (PgR)-negativity, and human epidermal growth factor receptor-related 2 (HER2)-negativity, is known to have the worst prognosis among the breast cancer subtypes [1, 2]. A pathological complete response (pCR) to neoadjuvant chemotherapy (NAC) using cytotoxic drugs, such as anthracyclines and

taxane, is considered a surrogate biomarker of a favorable prognosis, and additional treatment after both NAC and surgery reportedly improves the prognosis of non-pCR patients. However, recurrences have been reported in patients who have achieved pCR, indicating the need for more accurate predictive and prognostic biomarkers [3-5].

Originally, the *TP53* signature (*TP53sig*) was developed on the basis of various genes expressed in *TP53* structural mutant-type (MT) and wild-type (WT) breast cancers [6]. The *TP53sig* is a continuous, non-parametric value that can be used as a risk score. Previously, we reported that the overall prognosis of all subtypes of breast cancer could be predicted by setting a risk score cut-off for all subtypes and classifying each under the *TP53sig* MT or WT. When the *TP53sig* of all the subtypes was classified, most cases of TNBC were of the *TP53sig* MT [7]. Further, the molecular biology of the *TP53sig* was characterized by increasing genome instability and cancer cell cycle. Although each cancer subtype has already been examined in previous studies, TNBC is considered a heterogeneous population, and its response to NAC and its prognosis vary widely, as described above. Accordingly, TNBC was classified by the *TP53sig*, then predictive value of the *TP53sig-score* was assessed, and the NAC response and prognosis were analyzed according to the hypothesis that the *TP53sig* can be subclassified in detail even in a TNBC cohort. The present study also examined the molecular biological characteristics of patients with TNBC with a high *TP53sig-score* to consider new strategies for treatment.

Materials And Methods

Patient data from public databases

The cancer genome atlas program (TCGA) dataset was downloaded via cBioportal and Xena. [8-10] The Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) dataset was obtained from cBioportal.

Our own data

The medical records of 71 patients with TNBC who received neoadjuvant chemotherapy between January 2006 and December 2014 at Tokyo Metropolitan Cancer and Infectious Diseases Center at Komagome Hospital in Japan were retrospectively reviewed. Samples from 60 patients were analyzed for gene expression and clinicopathological data.

The patient data were collected in accordance with the ethical guidelines for medical and health research involving human subjects. Our protocol was approved by the institutional ethical committee (November 10th, 2018/ No. 2182) and was conducted according to the principles of the Declaration of Helsinki. All the patients provided informed consent in the form of opt-out.

RNA extraction

Glass slide specimens with 10- μ m thick sections of FFPE tissue block which were collected by core-needle biopsy or vacuum-assisted biopsy at the diagnosis were prepared. Total RNA was extracted from

the samples using RNeasy mini kit (Qiagen, USA)

Gene expression analysis via nCounter

RNA quality was monitored using NanoDrop 2000 (Thermo Fisher Scientific, Waltham, MA, USA). Without a poor extraction sample, we analyzed 60 FFPE specimens using digital quantification via the nCounter (NanoStrings Technologies, USA). A set of sixty genes including five internal control genes was used as the *TP53* signature gene set for nCounter. Following the manufacturer's instructions, we measured the expression values of the 33 genes using nCounter with 200 ng of total RNA extracted from the FFPE samples.

TP53sig-score

The *TP53sig-score* was calculated using micro array count data or nCounter according to the following formula. $TP53sig-score = (\text{sum of the count of 24 genes upregulated in tumors with a } TP53 \text{ mutation}) / (\text{sum of the count of nine genes downregulated in tumors with a } TP53 \text{ mutation})$.

Statistical analysis using clinical information

The association between various clinicopathological parameters and the *TP53sig-score* as determined using nCounter or microarray expression data was evaluated using the chi-square test or one-way analysis of variance (ANOVA) test. The t-test was used to analyze the expression data and the status of the *TP53sig-score*. The relapse-free survival (RFS) and breast cancer-free survival (BCFS) rates were calculated using the Kaplan–Meier method and evaluated using the log-rank test. RFS was defined as the period from the date of operation to the date of recurrence, and BCFS was defined as the period from the date of operation to the date of invasive breast cancer recurrence. For all statistical analyses, $p < 0.05$ was considered to indicate statistical significance. All statistical analyses were conducted using R ver3.32 (The R Foundation for Statistical Computing, Vienna, Austria <https://www.r-project.org/>) and EZR ver1.54 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R [11].

Gene ontology enrichment analysis

Gene Ontology (GO) enrichment analysis was performed using David ver6.8 [12, 13]. In the function annotation chart obtained from DAVID, GO terms with $p < 0.1$ were considered to indicate a statistically significance.

TIDE evaluation

Tumor Immune Dysfunction and Exclusion (TIDE) evaluation was performed via website platform (<http://tide.dfci.harvard.edu>) The TIDE score computed for each tumor sample can serve as a surrogate biomarker to predict the response to immune checkpoint blockade, including anti-PD1 and anti-CTLA4, for melanoma and NSCLC [14, 15].

Results

TP53sig-score for all breast cancer subtypes

We extracted 1904 stage I-III breast cancers from METABRIC and classified ER+ or PgR+ and HER2- as the luminal-type, ER+ or PgR+ and HER2+ as the luminal-HER2 type, ER-, PgR-, and HER2+ as the HER2-enriched type, and ER-, PgR-, and HER2- as the triple-negative type according to the results of ER/PgR/HER2 based on immunohistochemical (IHC) analysis of the four groups. When the *TP53sig* was compared in the last group, TNBC was found to have the highest score (Fig. 1; $p < 0.001$).

Patient characteristic for analysis and survival analysis in TNBC (METABRIC and our data)

In the present study, we analyzed our own data, including the TNBC-with-NAC and TNBC cohorts obtained from TCGA and METABRIC. As Table 1 shows, the *TP53sig* was calculated on the basis of expression data or microarray data, and the median of the *TP53sig-score* in each cohort was used to divide into the high and low *TP53sig* groups. Clinicopathological patient characteristics of these two groups did not differ significantly in either dataset. Both our own cohort and the METABRIC cohort tended to have a worse prognosis than individuals with a low *TP53sig-score* in the high *TP53sig-score* population although the difference was not significant (Figure 2; $p = 0.583$ and $p = 0.196$, respectively).

Survival analysis combining the TP53sig-score and NAC response

We analyzed the relationship between the *TP53sig-score* and NAC response in patients with TNBC. In terms of predicting the NAC response, the MKI-67 level was higher in the pCR patients (Figure 3A; $p = 0.0453$) whereas the *TP53sig-score* tended to be only slightly higher in the pCR patients although the difference was not statistically significant (Figure 3B; $p = 0.153$). In both the pCR and non-pCR patients, patients with a high *TP53sig-score* group tended to have a poor prognosis (Figure 4A; $p = 0.0739$). The MKI-67 scores, on the other hand, showed no such tendency (Figure 4B; $p = 0.734$). In addition, when the *TP53sig-score* was combined with the NAC response, the five-year breast cancer-free rate was found to be significantly different among the four groups (Table 2A, 2B ; $p = 0.043$).

Differentially expressed genes (DEGs) in the low and high TP53sig-score groups and evaluating tumor immunity environment using TIDE

DEGs in the high and low *TP53sig-score* groups in the TCGA were identified, and 498 DEGs with $P < 0.1$ and < 2 -fold change were detected. Many of these genes were related to GO terms, such as “cell differentiation” (e.g., DAPL1, USH1C, TEX15, DLK1, EDAR, SLC22A16, ZIC2, NHLH1, ELF5, SFRP5, SMOC1, PRAME, NKX2-5, KRT6A) and “innate immune response (e.g., DEFB1, IL27, MARCO, CLEC4C, SLPI, CLEC6A, NLRP2, LCN2, CD300E, IL36RN, S100A9, S100A8, S100A7, IGHV1OR21-1) in the high *TP53sig-score* group.

Tumor immunity was assessed using TIDE, a tool for predicting the effects of an immune checkpoint inhibitor (ICI), and was compared between the high and low *TP53sig-score* groups. In the METABRIC cohort (Figure 5A-F), high *TP53sig-score* group was associated with a higher proportion of responders ($p = 0.00253$), and the TIDE score predictive of T cell exhaustion was significantly low ($p < 0.001$). Moreover,

the CD274 scores related to PD-L1 expression were high ($p < 0.0454$). Expression profiles of cancer-associated fibrosis (CAF) and tumor-associated macrophages (TAMs) were also significantly low ($p < 0.001$ and $p = 0.0124$, respectively). On the other hand, an expression profile of myeloid-derived suppressor cells (MDSCs) was significantly high ($p < 0.001$). The TCGA cohort (Figure 5G-L) showed a similar trend to that of the METABRIC cohort, but except for CAF, the difference was not statistically significant.

Discussion

In the present study, TNBC was associated with a high *TP53sig-score* and the high *TP53sig-score* group was in turn associated with a poorer prognosis than the low *TP53sig-score* groups. Regardless of the NAC response, the high *TP53sig-score* group had a poor prognosis. The *TP53sig* was developed as a gene signature to predict structural mutations in *TP53*, but it was also found to reflect aspects of the tumor immune environment, such as TIDE, PD-L1, CAF, TAMs, and MDSCs.

Previous studies reported that *TP53sig-MT* was associated with a higher cell cycle, and that the expression signature, rather than the structural mutation of *TP53*, was useful in predicting the effect of FEC followed by paclitaxel in all breast cancer subtypes [7, 16]. In addition, the *TP53* MT type population reportedly has a high degree of nuclear atypia and Ki-67. In the present study, most of the TNBC *TP53* structural mutations and studies of the usual *TP53* MT type population showed that the *TP53sig-score* was inferior to MKI-67, which better reflects the cell cycle, but that a combination of the NAC response and *TP53sig* was better able to predict the prognosis.

The present study found that there was a high proportion of MDSCs in the high *TP53sig-score* group. The MDSC increases in cancer, inflammation, and infections and inhibit the T-cell response and has also been identified as a predictor of resistance to anticytotoxic T-lymphocyte-associated protein (CTLA4) antibodies in melanoma [17, 18]. The MDSC is also reportedly a poor prognostic marker of breast cancer, suggesting that it may be one of the causes of the poor prognosis of the high *TP53sig-score* population [19]. In vivo studies of breast cancer have reported that doxorubicin induced a reduction in MDSCs and that in other cancer species, 5-fluorouracil (5-FU) administration induced a decrease in MDSCs [20, 21]. Based on these results, the 5-FU and doxorubicin regimens may be a viable therapeutic option for the high-MDSC population, and of the 5-FU regimens, capecitabine may have the potential to be an effective treatment for high-risk TNBC, including cases with non-pCR [5].

The MT-type *TP53* signature is reportedly associated with a high PD-L1 level [7]. In addition, the structural mutation of *TP53* itself is also associated with PD-L1 expression, and genomic instability is a predictor of ICI efficacy [22-25]. ICIs are also thought to be effective against TNBC, especially cases with a high *TP53sig-score*.

The anti-PD-L1 and anti-PD-1 antibodies are reportedly useful not only against TNBC metastases but also in the perioperative period [26-28]. PD-L1 expression in IHC assays and microsatellite instability is the only predictive biomarker of efficacy, and more detailed biomarkers are needed [29]. TIDE was developed

as a tool to calculate T cell exhausted as well as PD-L1 expression and predict the effect of ICIs and expression profiles of CAF, TAM and MDSCs. The predominant effect of CAFs and TAMs is reportedly immunosuppressive roles in reducing T cell responses and regulating the killing effect of T cells and natural killer cells[30-32]. The present study suggested that the high *TP53sig-score* and usual non-pCR population in TNBC had a poor prognosis whereas the high *TP53sig-score* population had a low TIDE score and T-cell function. High PD-L1 expression also predicted a favorable response to ICIs, and patients with this feature are considered good candidates for ICI therapy.

In the present study, ICI efficacy was not directly investigated, nor was the tumor immune environment evaluated owing to the limited data available from nCounter for patients receiving NAC. However, two, large, public databases, TCGA and METABRIC, found similar results for the tumor immune environment, suggesting that the high *TP53sig-score* group among patients with TNBC may be good candidates for ICI therapy.

In conclusion, combining the NAC response with the *TP53sig-score* was able to predict a poor prognosis in patients with TNBC, and the high *TP53sig-score* population was found to have a favorable feature associated with immunotherapy response.

Declarations

Funding and competing interests

The authors declare that no funds, grants, or other support were received during the preparation of this manuscripts and have no relevant financial or non-financial interests to disclose.

Author contributions

M.O, S.Y. designed the study. M.O., T.A. and SI.H. reviewed clinical and pathological information. M.H. and S.Y. advised RNA extraction protocol and using nCounter. M.O. and S.Y. performed the statistical analyses. M.O. wrote the manuscript. S.Y. and S.K. critically revised the manuscript. All authors read and approved the manuscript.

Data availability

The data that support the findings of the present study are openly available in Gene Expression Omnibus (GEO) at <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE190275>, reference number GSE190275.

Ethics approval

Our protocol was approved by the institutional ethical committee of Tokyo metropolitan cancer and infectious diseases center Komagome hospital (November 10th, 2018/ No. 2182) and was conducted according to the principles of the Declaration of Helsinki.

All the patients provided informed consent in the form of opt-out.

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Tables

Tables 1 and 2 are available in the Supplemental Files section

Figures

Figure 1

The *TP53* signature score per TNBC subtype from METABRIC. The TNBC cohort had a higher *TP53* signature score than the other subtypes ($p < 0.001$).

Figure 2

Relapse-free survival analysis compared of the high and low *TP53*signature score groups in METABRIC (A) and our own data (B). Both cohorts tended to have a worse prognosis than individuals with a low *TP53*sig score in the high *TP53*sig score population although the difference was not significant ($p=0.583$ (A) and $p=0.196$ (B)).

<A>

Figure 3

Association of NAC effect and MKI-67 status (A) and *TP53* signature score (B). The MKI-67 level was higher in pCR patients ($p=0.0453$) whereas the *TP53*sig score tended to be slightly higher in pCR patients ($p=0.153$).

Figure 4

Relapse-free survival analysis compared among each group combined of NAC response and MKI-67 status (A) and *TP53* signature score (B). In both pCR and non-pCR patients, patients in the high *TP53*sig score group tended to have a poor prognosis (Figure 4A; p=0.0739).

Figure 5

Tumor immunity evaluation in high and low *TP53*sig groups based on data from METABRIC(A-F) and TCGA(G-L) compared with TIDE (A, G), interferon-gamma (B, H), CD274 (C, I), CAF (D, J), TAM (E, H) and MDSC (F, L). METABRIC cohort showed, in high *TP53*sig group the TIDE score predictive of T cell exhaustion was significantly low ($p < 0.001$), the CD274 scores related to PD-L1 expression were high ($p < 0.0454$), cancer-associated fibrosis (CAF) and tumor-associated macrophages (TAMs) were also significantly low ($p < 0.001$ and $p = 0.0124$). On the other hand, myeloid-derived suppressor cells (MDSCs) were significantly high ($p < 0.001$). The TCGA cohort (Figure 5G-L) showed a similar trend to that of the METABRIC cohort, but except for CAF, the difference was not statistically significant.

Supplementary Files

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