Lymphocyte Invasion in IC10/Basal-Like Breast Tumors Is Associated with Wild-Type TP53

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Abstract

Lymphocytic infiltration is associated with better prognosis in several epithelial malignancies including breast cancer. The tumor suppressor TP53 is mutated in approximately 30% of breast adenocarcinomas, with varying frequency across molecular subtypes. In this study of 1,420 breast tumors, we tested for interaction between TP53 mutation status and tumor subtype determined by PAM50 and integrative cluster analysis. In integrative cluster 10 (IC10)/basal-like breast cancer, we identify an association between lymphocytic infiltration, determined by an expression score, and retention of wild-type TP53. The expression-derived score agreed with the degree of lymphocytic infiltration assessed by pathologic review, and application of the Nanodissect algorithm was suggestive of this infiltration being primarily of cytotoxic T lymphocytes (CTL). Elevated expression of this CTL signature was associated with longer survival in IC10/Basal-like tumors. These findings identify a new link between the TP53 pathway and the adaptive immune response in estrogen receptor (ER)–negative breast tumors, suggesting a connection between TP53 inactivation and failure of tumor immunosurveillance.

Implications: The association of lymphocytic invasion of ER-negative breast tumors with the retention of wild-type TP53 implies a novel protective connection between TP53 function and tumor immunosurveillance. Mol Cancer Res; 13(3); 493–501. © 2015 American Association for Cancer Research.

Introduction

TP53 mutations occur in nearly 30% of breast cancers and are associated with worse survival and response to doxorubicin therapy (1–4). Breast cancer has been divided at the molecular level into five intrinsic subtypes (luminal A, luminal B, HER2-enriched, normal-like, and basal-like) using mRNA expression

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Note: Supplementary data for this article are available at Molecular Cancer Research Online (http://mcr.aacrjournals.org/).

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and ER-positive/HER2-positive breast tumors is associated with significant reductions in relative risk of death from disease (20–26). We recently reported that breast tumors with a higher ratio of TΦ1 to TΦ2-associated pathway activity had better outcome (21, 27). It is not known why immune cells infiltrate some tumors and not others. Here, we demonstrate an association between retention of wild-type TP53 (TP53-WT) alleles and increased infiltration of CTL in ER-negative tumors but not ER-positive tumors, linking these two phenomena and suggesting a subtype-specific link between TP53 function and immunosurveillance.

Materials and Methods

Data acquisition
Microarray measurements of tumor mRNA expression and DNA copy number from the METABRIC study were obtained from the European Genome-phenome archive (accession EGAS000000000083) and from GEO accession GSE3494. Illumina Human WG version 3 probe annotations were downloaded from the ReMOAT Illumina annotation (ref. 28). We determined 26,915 probes to be expressed above background. TP53 sequence was assessed by manual review of Sanger sequencing results as described in ref. 3, with 1,420 tumors successfully assessed for mutation status. Tumor infiltration scores were published by Silwal-Pandit and colleagues (3). Tumors were assessed by review of hematoyxlin and eosin–stained tissue sections by a pathologist. Tumors with scattered, discrete lymphocytes were scored as mild, and tumors with confluent sheets of lymphocytes were scored as severe. TP53 loss of heterozygosity was scored by assessing DNA copy number at the TP53 locus using the ASCAT algorithm (29). Both gene expression and TP53 mutation status were available for 1,420 tumors. All of infiltration score, TP53 mutation status, and gene expression data resulting in a successful PAM50 tumor subtype call were available for 1,086 tumors.

Statistical analysis
Statistical calculations were performed in R (30). Interaction between TP53 status and PAM50 assignment was tested by ANOVA in the discovery and validation cohorts separately. Interaction in the METABRIC data was considered significant if $P_{\text{interaction}} \leq 0.05$ after multiple testing correction by Holm adjustment for 26,915 tests. ANOVA models were assessed by visual inspection of Q-Q plots and of plots comparing residual versus fitted values. We obtained nonparametric $P$ values for ANOVA results by testing the interaction between TP53 status and PAM50 assignment in 1,000 permutations of the sample ordering for each probe while maintaining the original TP53 and tumor subtype factor ordering (31, 32). Nonparametric $P$ values for each probe were derived from the rank of the observed parametric $P$ value in a sorted list of $P$ values from permuted data for that probe. Linear models in the Miller dataset were constructed as for METABRIC, but with ER status rather than PAM50 subtype as the parameter interacting with TP53 mutation status. Results in the Miller dataset were considered statistically significant if $P_{\text{interaction}} < 0.05$ after multiple testing correction by Holm adjustment for 103 tests.

Survival analysis log rank tests were considered significant at $P < 0.05$. Gene Ontology enrichment analysis was performed using the BINGO package (33). Pathway enrichment was tested using QuSAGE, a gene set enrichment test that produces probability distributions for enrichment scores and corrects for correlation between genes within a gene set (34). The FDR values for QuSAGE were calculated using the Benjamini–Hochberg as implemented by the p.adjust function in R. Individual CTL, TΦ1, and TΦ2 scores for each tumor were generated by calculating the standardized expression for genes on each list and taking the mean of those values.

Gene pathway analysis
Gene lists derived from flow-cytometry separation of lymphocytes were obtained from results published in ref. 35. Nanodissection was performed as described in ref. 36; briefly, nanodissect uses a support vector machine within an iterative framework to handle standards of varying specificity. To derive gene lists, this method was applied on a diverse compendium of human microarray data with hand-curated immune markers for CTL, TΦ1, and TΦ2 cells. Each of the 69,708 samples in the compendium was processed from CEL files using RMA background correction.

Table 1. Summary of TP53 mutation and lymphocyte infiltration status

<table>
<thead>
<tr>
<th>TP53 status</th>
<th>Overall</th>
<th>WT</th>
<th>Mutant</th>
<th>Absent</th>
<th>Mild</th>
<th>Severe</th>
<th>No call</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER-positive</td>
<td>1,010 (78)</td>
<td>906 (82)</td>
<td>195 (18)</td>
<td>324 (37)</td>
<td>471 (54)</td>
<td>75 (09)</td>
<td>231</td>
</tr>
<tr>
<td>ER-negative</td>
<td>379 (22)</td>
<td>120 (39)</td>
<td>199 (62)</td>
<td>66 (28)</td>
<td>89 (58)</td>
<td>78 (54)</td>
<td>86</td>
</tr>
<tr>
<td>Luminal A</td>
<td>507 (36)</td>
<td>460 (91)</td>
<td>47 (09)</td>
<td>186 (44)</td>
<td>218 (52)</td>
<td>15 (04)</td>
<td>38</td>
</tr>
<tr>
<td>Luminal B</td>
<td>379 (27)</td>
<td>285 (75)</td>
<td>94 (25)</td>
<td>105 (35)</td>
<td>156 (52)</td>
<td>39 (13)</td>
<td>79</td>
</tr>
<tr>
<td>Normal-like</td>
<td>156 (10)</td>
<td>121 (89)</td>
<td>15 (11)</td>
<td>23 (21)</td>
<td>71 (66)</td>
<td>13 (12)</td>
<td>29</td>
</tr>
<tr>
<td>HER2-enriched</td>
<td>161 (10)</td>
<td>75 (47)</td>
<td>86 (55)</td>
<td>37 (33)</td>
<td>46 (41)</td>
<td>29 (26)</td>
<td>49</td>
</tr>
<tr>
<td>Basal-like</td>
<td>234 (17)</td>
<td>82 (35)</td>
<td>152 (65)</td>
<td>38 (23)</td>
<td>68 (42)</td>
<td>57 (55)</td>
<td>71</td>
</tr>
</tbody>
</table>

NOTE: Values are counts (percentage where present).
Figure 1. TP53 mutation status is associated with gene expression in basal-like tumors. A, heat maps showing standardized expression levels (left) and relative fold change (right) of 124 probes with significant interaction between TP53 status and PAM50 subtype in both METABRIC discovery and validation cohorts. TP53-WT tumors labeled "WT"; TP53-mutant tumors labeled "mut." Darker red, higher expression; darker blue, lower expression. Probes were plotted in the same order, sorted by the magnitude of fold change in basal-like tumors (see Supplementary Table S1). B, effect plots of expression of CCR7, CD2, CD3E, LY9, and perforin (PRF1) grouped by PAM50 subtype and TP53 mutation status. TP53-WT plotted in black; TP53-mutant plotted in blue. Points indicate mean; error bars, 95% CIs calculated from twice the SE. C, using data from Miller et al., effect plots of expression of CCR7, CD2, CD3E, LY9, and perforin (PRF1) grouped by ER status and TP53 mutation status show significant interaction as in the METABRIC data set. Drawn as in Fig. 1B.
Results

Basal-like TP53-WT tumors preferentially expressed cytotoxic T-cell markers

We analyzed gene expression and TP53 mutation status in the METABRIC cohort of patients with breast cancer, data previously reported in refs. 3, 10. The METABRIC cohort consists of separate discovery and validation subsets. We obtained both TP53 mutation status and gene expression microarray results for 803 and 617 patients in the discovery and validation sets, identifying 218 and 176 TP53-mutant tumors, respectively. ER-negative tumors were significantly more likely to harbor a TP53 mutation than ER-positive tumors (P < 0.001, Fisher exact test, Table 1). Because TP53 mutation is associated with worse survival in luminal B, normal-like, and HER2-enriched tumors but not basal-like tumors (3), we hypothesized that alterations in TP53 function due to TP53 mutation would have distinct effects on gene expression in the different intrinsic subtypes. Such differences might help explain the apparent absence of association between TP53 mutation and survival in basal-like tumors.

We therefore constructed a linear model for expression of each gene that included three terms: TP53 mutation status, PAM50 subtype, and the interaction between these terms (see Materials and Methods). We identified 219 probes with significant interactions in the discovery cohort and 548 probes in the validation cohort. These lists had 124 probes in common, comprising 103 genes (listed in Supplementary Table S1). A larger percentage of the tumors in the validation cohort with known TP53 mutation status were basal-like (22% in the validation cohort vs. 12% in the discovery cohort), which may explain why more significant interactions were identified in this cohort.

For some probes, residual values were not normally distributed or had heteroscedastic variance between strata, conditions which would violate the assumptions of the ANOVA (Materials and Methods). To test whether our findings were robust to these issues, we performed a nonparametric permutation analysis of interaction significance for the discovery and validation sets (see Materials and Methods). Probesets with the strongest P value for interaction in the parametric ANOVA also had the most significant P value for interaction as assessed by permutation analysis (Supplementary Fig. S1). We found 358 probes (314 genes) to be significant at P < 0.001 in both cohorts using the permutation approach, including all but one of the 103 genes identified by the parametric approach (TESPA1), supporting our finding that interaction between TP53 mutation status and tumor subtype was statistically significant for these genes.

The main effect identified in both cohorts by this analysis was upregulation of immune-related genes in the basal-like TP53-WT subgroup, as compared with TP53-mutant tumors (Fig. 1A). Genes with significant interactions between subtype and TP53 mutation status usually had strongly correlated expression (median Spearman rho = 0.64), and pathway analysis by Gene Ontology enrichment testing showed that this gene list was significantly enriched for genes with roles in regulation of T-cell activation, T-cell receptor signaling, and T-cell costimulation (corrected P < 2 \times 10^{-10}). These included T-cell surface antigens (e.g., CD2, CD3D, CD4, CD6, LY9), effector molecules for cytotoxic T cells (e.g., perforin), genes important to the T-cell antigen receptor pathway (e.g., CD247 and ZAP70), and CXCR3, a chemokine receptor participating in tissue infiltration by T cells (ref. 37; Fig. 1B).

We next confirmed the association between elevated expression of T-cell markers and TP53 mutation status in ER-negative tumors in an independent, previously published cohort of 247 breast tumors (38). This cohort was smaller than METABRIC, reducing the statistical power to identify interactions. Although the mean difference in T-cell gene expression levels between ER-negative TP53-WT and TP53-mutant tumors was also smaller than what we observed in the METABRIC data, we confirmed significant interaction for 14 of the 103 genes identified in the METABRIC analysis, including CXCR3, CD2, CD3E, LY9, and IL2RG (P<sub>interaction</sub> < 4.9 \times 10^{-4}, Fig. 1C).
Cytotoxic T-cell mRNA expression correlated with lymphocytic infiltration assessed by histopathology

We assessed the degree to which elevated expression of T-cell genes was associated with the presence of immune cells by comparing expression of lymphocytic markers with lymphocytic infiltration scores (graded as absent, mild, or severe; see Materials and Methods). ER-negative tumors had significantly higher degrees of infiltration than ER-positive tumors ($P < 0.001$, $\chi^2$ test for trend) with the highest percentage of severe infiltration occurring in basal-like tumors (Table 1). Across all tumor subtypes, lymphocytic infiltration determined by histopathology was strongly correlated with expression of CD2, CD3E, CCR7, and other genes associated with lymphocytes (Fig. 2A).

CTL and T112 expression scores were higher in ER-negative and IC10/basal-like TP53-WT tumors than TP53-mutant tumors

For subsequent analysis, we calculated expression scores for CTL, T111, and T112 genes using two complementary approaches. We first generated CTL, T111, and T112 gene lists using Nanodissect, an in silico method to identify genes with cell-lineage-specific expression (ref. 36; gene lists in Supplementary Tables S2 and S3). The correlation between increases in lymphocyte infiltration assessed by histopathology and increased CTL score was strong (Fig. 2B). CTL score was correlated positively with T111 score ($r^2 = 0.49$, $P < 0.001$) and inversely with T112 expression score ($r^2 = 0.17$, $P < 0.001$). We identified a significant interaction between TP53 mutation status and tumor subtype associated with CTL score using the parametric ANOVA model ($P = 3 \times 10^{-13}$). The lowest $P$ value in 100,000 random sample permutations using this model was $4.8 \times 10^{-6}$, supporting our finding that the interaction between TP53 mutation status and tumor subtype was statistically significant for the CTL score. We obtained similar results using gene lists derived from gene expression microarray analysis of cell fractions obtained by flow-cytometry separation of lymphocytes (Supplementary Fig. S2; ref. 35).

We then compared these scores in TP53-WT and TP53-mutant tumors by pathway differential expression analysis (34). ER-positive TP53-mutant tumors had slightly lower T111 scores, whereas ER-negative TP53 wild-type tumors had significantly higher CTL scores and lower T112 scores (Fig. 3A). Within the intrinsic subtypes, no score was significantly different in luminal A or normal-like tumors, whereas TP53-mutant luminal B tumors had lower CTL and T111 scores (Fig. 3B). TP53-mutant HER2-enriched tumors had slightly lower T112 scores, whereas TP53-mutant basal-like tumors had higher CTL scores and lower T112 scores (Fig. 3B). Within the ICs, IC4 and IC10 had clearly higher CTL scores compared with other subtypes. IC4, which is enriched for tumors with heavy lymphocytic infiltration, on the basis of copy-number analysis (showing the deletions corresponding to T-cell receptor rearrangement), gene expression, and histological assessment, had the highest CTL score (Table 2; Supplementary Fig. S3). But, whereas IC10 tumors (which are basal-like tumors with genomic instability) that were TP53-WT had higher CTL and

Table 2. CTL expression scores

<table>
<thead>
<tr>
<th></th>
<th>CTL score (all)</th>
<th>CTL score (TP53-WT)</th>
<th>CTL score (TP53-mutant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER-positive</td>
<td>-0.91</td>
<td>-0.07</td>
<td>0.01</td>
</tr>
<tr>
<td>ER-negative</td>
<td>0.31</td>
<td>0.58</td>
<td>0.16</td>
</tr>
<tr>
<td>Luminal A</td>
<td>-0.19</td>
<td>-0.16</td>
<td>-0.06</td>
</tr>
<tr>
<td>Luminal B</td>
<td>-0.18</td>
<td>-0.18</td>
<td>-0.02</td>
</tr>
<tr>
<td>Normal-like</td>
<td>0.25</td>
<td>0.29</td>
<td>0.27</td>
</tr>
<tr>
<td>HER2-enriched</td>
<td>0.16</td>
<td>0.34</td>
<td>0.04</td>
</tr>
<tr>
<td>Basal-like</td>
<td>0.42</td>
<td>0.88</td>
<td>0.20</td>
</tr>
<tr>
<td>IC1</td>
<td>-0.06</td>
<td>-0.05</td>
<td>0.15</td>
</tr>
<tr>
<td>IC2</td>
<td>-0.08</td>
<td>-0.07</td>
<td>0.05</td>
</tr>
<tr>
<td>IC3</td>
<td>-0.02</td>
<td>-0.01</td>
<td>0.21</td>
</tr>
<tr>
<td>IC4</td>
<td>0.39</td>
<td>0.43</td>
<td>0.35</td>
</tr>
<tr>
<td>IC5</td>
<td>0.08</td>
<td>0.18</td>
<td>-0.02</td>
</tr>
<tr>
<td>IC6</td>
<td>-0.24</td>
<td>-0.22</td>
<td>-0.17</td>
</tr>
<tr>
<td>IC7</td>
<td>-0.22</td>
<td>-0.20</td>
<td>-0.08</td>
</tr>
<tr>
<td>IC8</td>
<td>-0.41</td>
<td>-0.36</td>
<td>-0.34</td>
</tr>
<tr>
<td>IC9</td>
<td>-0.08</td>
<td>-0.07</td>
<td>0.02</td>
</tr>
<tr>
<td>IC10</td>
<td>0.28</td>
<td>0.76</td>
<td>0.15</td>
</tr>
</tbody>
</table>
T11 scores and lower T12 scores, IC4 tumors (which have mostly flat genomic profiles) had no significant difference in CTL/T11/ T12 scores related to TP53 mutation status (Fig. 3C).

Both TP53 mutation and loss of heterozygosity correlated with CTL scores in IC10/basal-like tumors

There is evidence from biochemical analysis in vitro and in vivo that although many TP53 missense mutations result in loss of function or exert dominant-negative effects, some result in gain of function (reviewed in ref. 39). Truncating mutations in TP53 (e.g., premature stop codons), which inactivate the protein, were more frequent in basal-like and HER2-enriched tumors (3). Nevertheless, after adjusting for subtype, we did not identify a significant correlation between immune scores and TP53 mutation type (data not shown).

If TP53 loss of heterozygosity (TP53-LOH) could phenocopy TP53 mutation, we would expect TP53-LOH would also be associated with lower CTL scores. To test this, we fitted a linear model for CTL score using TP53-LOH status, TP53-mutation status, and the interaction between TP53-LOH and TP53-mutation status as terms. TP53-WT tumors with copy-number neutral LOH were counted as TP53-LOH, as these tumors had lower expression of TP53 mRNA than TP53-WT tumors without LOH (Supplementary Fig. S4).

In ER-negative, basal-like, and IC10 tumors, both TP53 mutation and TP53-LOH were associated with lower CTL scores when evaluated as a single factor (P < 0.001) and after adjusting for the effect of the other factor (P < 0.05; Fig. 4A–C). Neither factor was significant in ER-positive tumors or normal-like tumors. After stratifying HER2-enriched tumors by ER status, both TP53 mutation and TP53-LOH were significantly and independently associated with CTL score in ER-negative, but not ER-positive, tumors (P < 0.05; Supplementary Fig. S5). In IC4 tumors, TP53-LOH but not TP53-mutation status was associated with lower CTL score (P < 0.05; Fig. 4D). We did not find evidence for a statistical interaction between these two factors in any subgroup. In cases where both associations were significant, the decrease in CTL score associated with TP53-LOH was larger than that associated with TP53 mutation (Fig 4A–C).

Elevated CTL expression score was associated with better survival in IC10/basal-like tumors

Several previous reports have found an association between elevated expression of immune cell genes and/or lymphocytic infiltration and better survival in basal-like or ER-negative tumors (refs. 20, 22–26). We divided samples into four quartiles by their CTL scores and compared survival of patients in the highest quartile (the highest CTL scores) with those in the other three quartiles (Materials and Methods). In a univariate survival analysis, we found a significant association between higher CTL score and longer disease-specific survival in ER-negative [P = 0.001, OR = 0.61; confidence interval (CI), 0.45–0.82; log-rank test, Fig. 5A].
but not ER-positive, tumors (Fig. 5B). We found a similar result for basal-like tumors ($P = 0.005$, OR = 0.59; CI, 0.41–0.86, log-rank test, Fig. 5C) but not HER2-enriched tumors (Fig. 5D). The effect was statistically strongest in IC10 tumors ($P = 4 \times 10^{-5}$, OR = 0.35; CI, 0.20–0.60, log-rank test, Fig. 5E) and not significant in IC4 (Fig. 5F). This effect was significant in ER-negative, basal-like, and IC10 tumors after correction for the presence of lymph node metastasis, which was the strongest prognostic feature in METABRIC ($P < 0.05$, log-rank test). In contrast, TP53 status did not provide independent prognostic information in any of these groups in univariate analysis or after adjusting for elevated CTL expression.

**Discussion**

This study presents association analysis of two independent cohorts supporting a link between TP53 status in breast tumors and CTL expression. The expression-based CTL score, used here as a surrogate of lymphocytic infiltration, was higher in TP53-WT versus mutant ER-negative, basal-like, and IC10 breast tumors. Women with basal-like breast tumors and a high CTL score had significantly longer survival. This effect was strongest in the "core" basal-like tumors from IC10. The best-understood model for TP53-mediated tumor suppression involves its induction by DNA damage to induce apoptosis or cell-cycle arrest through transcriptional activation of genes controlling these processes (40). TP53 function can be impaired by truncating mutations, missense mutations affecting its DNA-binding motif, somatic loss of one or both copies of a TP53-WT allele, or indirect effects such as binding of the TP53 protein to viral proteins or proteins such as MDM2. Our results suggest that the interaction with TP53 that we observed was attributable to loss of a TP53-WT allele rather than a new TP53-mutant–specific function.

Direct evidence for a mechanistic link between TP53 and immunosurveillance will require additional functional studies. It may be that CTL function is influenced by the TP53 pathway status of tumor cells that are targeted for apoptosis. The primary mechanism for CTL-mediated cell death is induction of apoptosis via the caspase cascade, suggesting that abrogating the TP53 pathway may provide an added benefit to tumor cells in escaping CTL-mediated apoptosis. Studies from the Chouaib lab (41) using a TP53-WT melanoma cell line paired with an autologous CTL line have shown evidence for a direct link between TP53 and CTL function in killing tumor cells. That study showed that granzyme B-mediated tumor cell death was inhibited by knocking down TP53 expression with siRNA or by treatment with the TP53 inhibitor pifithrin-alpha, and conjugation between CTLs and their targets leads to TP53 protein accumulation (41). These results are compatible with a direct functional link between TP53-mediated apoptosis and CTL function, but independent replication in breast cancer cells is needed to establish whether this model is relevant to basal-like tumors.

A failure of immunosurveillance to arrest tumor development (“immune escape”) can occur by several routes. Some tumors stop
producing antigens recognized as foreign by the adaptive immune system. Others deactivate the apoptotic pathways triggered by T-cell response. Our data suggest that CTL-mediated immunosurveillance is more effective in ER-negative breast tumors if the tumor still expresses wild-type TP53, and that tumors losing TP53-WT alleles gain a selective advantage in part by more successfully evading the adaptive immune system.

Disclosure of Potential Conflicts of Interest

C. Vaske is Chief Scientific Officer at Five3 Genomics and is also Executive Vice President, Genomic Research, at NantOtics. He also has ownership interest (including patents) in Five3 Genomics and NantOtics. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions

Conception and design: C. Caldas, A.-L. Barresen-Dale, V. Kristensen

Development of methodology: C. Vaske, O. Troyanskaya, C. Caldas, A.-L. Barresen-Dale

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): D. Quigley, L. Silwal-Pandit, R. Dannenfelser, A. Langerod, H.K.M. Vollan, C. Vaske, O. Troyanskaya, C. Caldas, A.-L. Barresen-Dale, V. Kristensen

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