Relationship of the Breast Ductal Carcinoma In Situ Immune Microenvironment with Clinicopathological and Genetic Features

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Abstract

Purpose: The immune microenvironment of breast ductal carcinoma in situ (DCIS) has yet to be fully explored, and the relationship of immune cells to genetic features of DCIS is unknown.

Experimental Design: We quantified tumor-associated lymphocytes (TIL) and evaluated PD-L1 protein levels by immunohistochemistry in a cohort of pure DCIS (138 and 79 cases, respectively), some of which had copy number (n = 55) and mutation data (n = 29).

Results: TILs were identified in the stroma surrounding DCIS (119/138, 86%) and present at a median TIL score of 5% (range, 0%–90%). Most DCIS were negative for tumor cell PD-L1 staining (89%), but 25% of cases were positive for immune cell staining. We observed that, as in invasive breast cancer, TILs and PD-L1 positivity were significantly greater in high-grade (P = 0.002/0.035), ER-negative (P = 0.02/0.02), and ERBB2-amplified tumors (P < 0.001/0.048). Comedo necrosis was significantly positively associated with TILs (P < 0.0001) but not with PD-L1. The TILs score was significantly higher in cases with TP53 mutation (P = 0.03) but not with PIK3CA or GATA3 mutation. In the cases with copy number data, both the fraction of the genome altered and the number of telomeric imbalances were significantly positively correlated with TILs (both P < 0.001). This result strongly contrasted with invasive breast cancer data, where aneuploidy was not correlated to TIL levels.

Conclusions: Although a small cohort, our data suggest a preliminary model by which the progression of DCIS to invasive carcinoma may involve an altered relationship of tumor copy number with the immune microenvironment, possibly by the immunoeediting of the tumor.

Introduction

It is increasingly recognized that the host immune response to cancer is important in disease progression and response to treatment (1). The presence of a robust immune response in triple-negative and HER2-positive invasive breast carcinoma, as determined by scoring of tumor-infiltrating lymphocytes (TIL) on hematoxylin and eosin (H&E)-stained sections, is associated with favorable prognosis and improved response to neoadjuvant chemotherapy (reviewed in ref. 2) and in the adjuvant setting to docetaxel, trastuzumab, and pertuzumab (3). It has been suggested that the immune response in invasive breast cancer and other tumor types may correlate with mutational load due to the potential for neoantigen formation (4) or, alternatively, with the specific mutational signature (5). Higher TILs are consistently seen in triple-negative breast cancers, followed by HER2-positive cancers, with high TIL scores observed only rarely in luminal cancers (6).

The host immune response to tumors has gained prominence following the recent successes of immune checkpoint inhibitor therapies (7, 8). Immune checkpoint molecules, including PD-L1 and CTLA-4, function to induce tolerance to self-antigens and prevent overactivation of the adaptive immune response (7, 9). PD-L1 can be expressed both on tumor cells and in infiltrating immune cells and may correlate with favorable prognosis and response to immune checkpoint inhibitor therapy in diverse tumor types including non–small cell lung carcinoma, melanoma, and urothelial carcinoma (10–14). PD-L1 expression in invasive breast carcinomas is most common in tumor cells in triple-negative cancers and correlates closely with the extent of the immune infiltrate (15, 16).

Ductal carcinoma in situ (DCIS) represents a noninvasive or preinvasive form of breast carcinoma. Prediction of those cases of DCIS likely to progress to invasive carcinoma is imprecise.
Translational Relevance

Understanding the drivers of progression of breast ductal carcinoma in situ (DCIS) to invasive breast carcinoma is a key unanswered question in breast cancer with great translational relevance, given the high frequency of DCIS diagnoses in the mammographic screening era and the lack of robust biomarkers. Escaping the host immune response could be critically important, thus we assessed the immune milieu of DCIS and correlated this for the first time with the genomic characteristics of the tumor. We found that, unlike invasive breast cancer, levels of genomic copy number change in DCIS correlate positively with the presence of immune cells. Progression to invasive disease may therefore require copy number–driven immunoediting and suggest that a combination of copy number and immune-cell markers could be evaluated as potential biomarkers of invasive potential.

Materials and Methods

DCIS cohorts

Cases were obtained from the Peter MacCallum Cancer Centre (PMCC), the University of Queensland Centre for Clinical Research (UQCCR), and the Royal Melbourne Hospital (RMH). Approval for the study was obtained from the ethics committees of Peter MacCallum Cancer Centre (project numbers 02/26, 10/16, and 00/81) and the University of Queensland (project UQ HREC 2005000785). Participants from RMH provided written informed consent; however, waiver of consent was approved for tissues obtained under ethical approval (n = 887 with associated Level 3 Affymetrix SNP6 copy number data) using the “biospecimen_slide_brca” file, excluding those with 0% tumor and averaging the TILs from cases with more than one slide.

IHC

Three-micron formalin-fixed paraffin-embedded tissue sections were stained on the Ventana BenchMark ULTRA system using Ventana PD-L1 (SP263) Rabbit Monoclonal Primary Antibody as per the recommended protocol. Sections were deparaffinized and antigen retrieval was performed with Cell Conditioner 1 (CC1) for 64 minutes. Sections were then incubated with the primary antibody for 16 minutes at 36°C, followed by the OptiView HQ Linker for 8 minutes and the OptiView HRP Multimer for 8 minutes. Counterstaining was performed with Mayer’s hematoxylin and Scott’s tap water bluing reagent. Human tonsillar and placental tissues were used as positive controls.

PD-L1 was considered to be positive when any perceptible membranous staining was present in at least 1% of tumor cells, and, in immune cells when at least 1% of the tumor specialized stroma containing involved ducts contained PD-L1–positive immune cells. Staining associated with comedo necrosis or biopsy site was excluded.

Statistical and data analysis

Copy number analysis was performed as previously described (refs. 18, 23). Fraction of the genome altered (FGA) was calculated as the percentage of base pairs with copy number gain or loss. Number of telomeric allelic imbalances (NTAI) was calculated as the count of telomeres (excluding chromosome Y) with a gain or loss.

Statistical analyses were performed in R, including Fisher exact tests, two-sample Wilcoxon rank sum tests, one-way analysis of variance (ANOVA) and Cox regression (log-rank test). All tests were two-sided. Tukey multiple comparison posttests were performed after ANOVA. Statistical significance was determined as P values of <0.05.

Results

Analysis of TILs with DCIS clinicopathologic parameters

We assessed the presence of TILs in the surrounding stroma of 138 cases of DCIS. The presence of TILs ranged from 0% to 80% (median, 20%), with TILs > 15% in 45% of cases. The median percentage of TILs in DCIS cases was significantly higher than that in invasive carcinoma cases (20% vs. 15%, P = 0.007). The presence of TILs was associated with lower nuclear grade, lower hormone receptor expression, and comedo necrosis.

Immune Cells and Genomics in DCIS

Two tissue microarrays (TMA) were constructed containing (i) two 2-mm cores from 44 PMCC cases, and (ii) two 0.6-mm cores from 35 UQCCR cases, with 56 cases overlapping with the full section H&E study. Most cases were treated with wide local excision (57/79, 72%) with 24% treated by mastectomy. Radiotherapy was undertaken for 22 patients (28%), and five were treated with hormonal therapy (6%). Follow-up data were available for 76 cases (median length 3 years 2 months; range, 1 month–20 years 2 months), of which 21 (27.6%) had a recurrence (11 as DCIS and 10 as invasive).

Assessment of TILs

TILs were assessed on whole H&E-stained sections containing DCIS. The percentage stromal TILs, defined as the percentage of stromal area covered by mononuclear inflammatory cells, was estimated in the specialized stroma surrounding DCIS-containing ducts (21, 22). TIL data were obtained from TCGA invasive breast cancer data (n = 887 with associated Level 3 Affymetrix SNP6 copy number data) using the “biospecimen_slide_brca” file, excluding those with 0% tumor and averaging the TILs from cases with more than one slide.

Histopathologic factors such as nuclear grade, hormone receptor expression, and comedo necrosis and genomic alterations including copy number changes have been shown to correlate with disease progression (17, 18). Less is known about the immune response to DCIS and its potential prognostic significance. The concept of cancer immunoediting (19) suggests that tumors progressively develop mechanisms of immune evasion, such as loss of immunogenic antigens or the creation of an immunosuppressive microenvironment (19). Study of preinvasive lesions such as DCIS may provide interesting insights into immunoediting in breast carcinoma. In this study, we sought to investigate TILs and PD-L1 expression in DCIS and to correlate these parameters with clinicopathologic features and genomic information.
from a score of 0% to 90%, with a median of 5 and interquartile range of 1% to 15%. Nineteen cases had no TILs present (14%). Reports in invasive breast cancer have suggested that TILs are associated with certain tumor features, so we first evaluated similar features in DCIS (Table 1). The TIL score was significantly increased in high-grade tumors ($P = 0.002$), ER-negative tumors ($P = 0.002$), ERBB2-positive tumors ($P < 0.0001$) and tumors with necrosis ($P < 0.0001$; Fig. 1). TIL score was not significantly related to recurrence either as a continuous variable or when the TIL

<table>
<thead>
<tr>
<th>Feature</th>
<th>Number of cases</th>
<th>Median TIL score</th>
<th>$P^a$</th>
<th>Reported association in invasive breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclear grade</td>
<td></td>
<td></td>
<td></td>
<td>Higher TIL score found in grade 3 tumors (41)</td>
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<tr>
<td>Low</td>
<td>15</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>35</td>
<td>5</td>
<td></td>
<td></td>
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<tr>
<td>High</td>
<td>88</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comedo necrosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>90</td>
<td>10</td>
<td>&lt;0.0001</td>
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</tr>
<tr>
<td>No</td>
<td>48</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>ER status</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Positive</td>
<td>87</td>
<td>5</td>
<td>0.002</td>
<td>Lower TILs in hormone receptor negative tumors (reviewed in ref. 6)</td>
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<tr>
<td>Negative</td>
<td>17</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERBB2 status</td>
<td></td>
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<tr>
<td>Positive</td>
<td>29</td>
<td>20</td>
<td>&lt;0.0001</td>
<td>ERBB2 positive tumors display similar TIL levels to triple negative tumors (reviewed in ref. 6)</td>
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<tr>
<td>Negative</td>
<td>69</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease recurrence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>27</td>
<td>5</td>
<td>0.643</td>
<td>High TILs associated with improved recurrence-free survival in triple-negative and ERBB2-positive tumors after chemotherapy (24, 28, 42–44)</td>
</tr>
<tr>
<td>No</td>
<td>83</td>
<td>5</td>
<td></td>
<td></td>
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</table>

*aAll tests are Wilcoxon rank sum analyses apart from nuclear grade, which was assessed by one-way ANOVA. Bold values are statistically significant at $P < 0.05$. 

Figure 1. Clinicopathological associations of DCIS with TIL score. Corrected $P$ values; *, $P < 0.05$. 

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score was categorized into low (0 or 1, first quartile), intermediate (2–15, second and third quartiles), and high (>15, fourth quartile) categories.

Of the 27 DCIS cases with subsequent recurrence, we were able to obtain ipsilateral recurrence tissue for 8 cases (7 DCIS and 1 invasive carcinoma) and to score TILs in these tumors. The level of TILs was not significantly different (paired Mann–Whitney test \( P = 0.22 \)) but there was a trend for the recurrences to have fewer TILs than the primary tumor (Supplementary Fig. S2). The sole invasive recurrence had a TIL count of 1%, the same as the initial DCIS.

PDL1 tumor cell expression is rare in DCIS

Two TMA cohorts comprising 79 cases (from PMCC and UQCCR) were assessed for tumor cell (TC) and immune cell (IC) PD-L1 expression along with 20 whole sections from the PMCC cohort (Fig. 2). Concordance between whole sections and TMA was 87.5% (14/16): one whole section identified focal TC staining that was absent on the TMA core; another case showed focal IC and TC staining missing from the TMA core. Only 9 of 79 (11%) of DCIS cases showed any TC expression of PD-L1, which was predominantly weak and scattered with only one case showing expression in greater than 1% of tumor cells (Fig. 2C). In contrast, 20 of 79 (25%) showed PD-L1 expression in the IC compartment, predominantly staining lymphocytes associated with involved ducts (Fig. 2D). The majority of cases showing TC expression of PD-L1 also showed IC expression (6/9, 67%). PD-L1–expressing cases in either compartment were significantly more likely to be ER-negative (\( P = 0.019, 0.001 \) for TC and IC, respectively) and HER2 positive (\( P = 0.046, 0.002 \) for TC and IC, respectively; Table 2). Cases with PD-L1–positive TC were more significantly more likely to be high grade (\( P = 0.033 \)), but no significant correlation with grade was seen for IC PD-L1 expression (\( P = 0.19 \)). Comedo necrosis was not associated with PD-L1 expression. There was no significant association of PD-L1–positive staining with recurrence.

A subset of cases had both TIL and PD-L1 scoring (\( n = 56, 71\% \)). There was a positive correlation between expression of PD-L1 and TILs, with PD-L1–positive cases having a significantly higher mean TIL count for both TC (\( P = 0.03 \)) and IC compartments (\( P < 0.001 \)).

Genetic events and the immune response in DCIS

As the presence of genomic alterations may influence the immunogenicity of DCIS lesions, the presence of TILs was compared with existing genomic information. Copy number data were available for 55 cases across two cohorts (refs. 18, 23), and mutation data from a 107-gene targeted sequencing assay for 20 cases (23). There was no significant correlation of TILs with total mutation number (although the number of mutations was less than five per case), but we did observe a significant positive correlation in 55 cases between the presence of TILs and the FGA by copy number and the number of telomeric allelic imbalances (NTAI; one-way ANOVA \( P < 0.001 \) for both, Fig. 3). Overall, cases with low levels of TILs had a...
significantly lower FGA and lower NTAI compared with cases with high levels of TILs (P < 0.001, Tukey posttests for both). In contrast, invasive breast cancer cases from TCGA did not demonstrate a significant association between FGA and TIL levels (Fig. 3). Low TIL invasive breast cancer cases had a mean FGA of 24.3 (±15.95), while the mean FGA in high TIL cases was 20.4 (±17.1).

When comparing the percentage of TILs with specific genetic events, there was a significant correlation of high TILs with the presence of a TP53 mutation (P = 0.033, Mann–Whitney test, Fig. 3) and also with ERBB2 amplification (P = 0.001). No significant association was seen with PIK3CA or GATA3 mutations. In TCGA invasive breast cancer data, TP53 mutation was also associated with higher levels of TILs (P = 0.001).

Twenty cases had both mutation and full section PD-L1 IHC data. The NTAI score was significantly higher in cases with positive IC PD-L1 staining (P = 0.046; Fig. 3), and there was also a positive trend for TC PD-L1 staining (P = 0.098). There was a nonsignificant trend of TC PD-L1 positivity with TP53 mutation (P = 0.13), whereby 3 of 5 TC PD-L1–positive cases were TP53 mutant. There was no significant association with FGA, PIK3CA mutation or GATA3 mutation; however, these analyses were limited in power by the small number of cases available.

### Discussion

In this study evaluating the immune response to DCIS we have found a number of significant associations and for the first time correlated the immune microenvironment with genetic features of DCIS. We first assessed TILs on H&E sections, which is a reproducible, quick, and inexpensive method of evaluating the immune infiltrate in tumors (24, 25) and has been validated to show prognostic and predictive significance in invasive breast carcinoma (24). Using this method, we showed that, as in invasive breast carcinoma, TILs appear to be more prevalent in DCIS that is ER-negative. In addition, HER2-positive DCIS show a higher TIL score than HER2-negative DCIS. These findings are in agreement with previous studies of the immune microenvironment of DCIS, in which ER-negative tumors showed a trend towards higher immune infiltrates (22, 26, 27) and HER2 positive tumors were strongly associated with a higher stromal TIL count (22). Despite significant positive associations with histological features that portend a poor prognosis such as high nuclear grade, comedo necrosis, periductal myxoid stroma, ER negativity, and HER2 positivity, no significant association was found in our study between TILs and recurrence. Such a result could suggest a protective role of a robust immune infiltrate in high-risk DCIS; however, our study was inadequately powered to draw such a conclusion. Disease recurrence following DCIS can occur after many years, and although the TIL cohort was enriched for cases with recurrence (30/138, 21.7%) and had a prolonged median follow-up of 89 months (range, 1–304 months), the lack of association between TILs and recurrence requires further investigation in a large cohort with substantial length of follow-up to enable a well-powered multivariate analysis. One such study also failed to find a correlation between TILs and DCIS recurrence (22).

However, such analysis is complicated by the likely different implication of TILs in different intrinsic subtypes (28), the different types of lymphocytes present not distinguishable by H&E staining and the difficulty in getting enough cases to make subgroup analysis sufficiently powerful. In this recent study, even with a starting cohort of almost 1,500 DCIS cases, the number of cases with very high TIL infiltrate in the luminal A, luminal B/HER2+ and triple-negative groups was less than 10 each.

A limitation of the study was the restriction of performing TIL scoring on H&E only, thus information as to the functional status of the immune infiltrate was not obtained, and it is possible therefore that important associations may have been missed. Most of the TILs in DCIS are CD3+ T cells, with CD4+ T helper cells slightly outnumbering CD8+ cytotoxic T cells (27). We have previously demonstrated the prognostic significance of FOXP3+ regulatory T cell (Treg) infiltration in DCIS, with higher Treg infiltration associated with disease recurrence in patients with both pure DCIS and invasive disease, even after 5 years (29). In contrast, Campbell and colleagues found that only the combination of CD8, HLA-DR, and CD115 immunohistochemistry was predictive of recurrence in their DCIS series (26).

Overall, higher numbers of Tregs were found in DCIS than in normal breast tissue, with the highest number found in invasive breast carcinoma (29). Similar findings were reported by Lal and colleagues (30). Interestingly, Treg infiltration in pancreatic cancer also appears to increase from normal tissue to preinvasive lesions to invasive adenocarcinoma (31). The opposite pattern was found for cytotoxic CD8+ T cells, which decreased with malignant progression (31). These findings support the concept of a progressively immunosuppressive microenvironment allowing immune evasion and disease progression.

Second, we performed PD-L1 IHC in DCIS. In contrast to a previous study (27), PD-L1 expression by DCIS cells was rare in our cohort. Our use of the Ventana SP263 antibody, which in our hands is the most accurate of the commercially available.
available anti–PD-L1 IHC assays (unpublished data), may explain this difference. However, as previously reported (27), PD-L1 was predominantly expressed on the immune infiltrate. Immune cell PD-L1 expression in invasive breast carcinoma is more common than tumor cell PD-L1 expression, is associated with high-risk histological features such as tumor grade, and is more common in triple-negative carcinomas (15, 32–34). In our cohort of pure DCIS, we identified associations between
immune cell PD-L1 expression and ER negativity, but not with high-risk histological features such as high nuclear grade or comedo necrosis.

It is not yet conclusively known why some breast carcinomas have higher TILs than others. Polarization toward an immuno-suppressive microenvironment due to ER signaling has been suggested as one possibility to explain elevated TILs in ER-negative carcinomas (35). Another is the relationship with genetic aberrations, as in melanoma, because the overall mutational load is much higher in triple-negative than luminal subtype breast carcinomas, with higher potential for neoantigen formation (36). However, there is no evidence that mutational load directly correlates with TILs or immune signatures within breast cancer subtypes (37, 38). Mutations in specific oncogenes such as TP53 appear not to affect the immune response in invasive breast carcinoma (24), which is supported by our findings in DCIS where neither PIK3CA nor GATA3 mutations were related to TILs. We did observe a strong significant association with TP53 mutation; however, this could be confounded by the association of TP53 mutation with other features also associated with TILs such as high grade, ER negativity, and HER2 positivity. In invasive breast cancer, higher TILs have also been observed in TP53-mutant tumors (39), including within triple-negative invasive breast cancer (40). Specific mutational signatures have also been suggested to explain the wide variation in TILs seen in luminal breast cancers, with those displaying mutational signatures 3 or 13, corresponding to homologous recombination pathway defects and the APOBEC mutational pattern, respectively, showing the highest immune-infiltrates (5). Indeed, we observed a positive correlation between both TILs and PD-L1 positivity and one measure of homologous recombination deficiency, the NTAI.

Surprisingly, we observed a significant association with the presence of TILs and the fraction of the genome altered by copy number in pure DCIS that has not been identified in invasive breast cancer data. Although this observation needs to be replicated in a cohort where DCIS and invasive cancer are scored for both parameters using the same methods, it suggests several intriguing possibilities. First, that the presence of TILs in the stroma surrounding DCIS could be influenced by the antigens produced by copy number variation, a major driver in breast cancer. Second, the change in the immune environment when TILs come into widespread direct contact with the carcinoma cells may lead to immunoediting of the tumor based on copy number or moderation of the immune environment by the tumor. Intriguingly, a recent pan-cancer analysis of TILs and copy number suggested that high levels of aneuploidy are correlated with a low immune gene expression profile (38). In particular, the CD8+ T cell signature was reduced in invasive breast carcinomas with high aneuploidy. This suggests that the evasion of the immune system could be a key event in the progression of DCIS to invasive breast carcinoma and requires tumor immunoediting driven by copy number change to remove neoantigens. Finally, the combination of low-FOA/low NTAI and low TILs could indicate a DCIS type that is unlikely to progress to invasive disease, and is therefore seldom observed in invasive cohorts. This possibility would be consistent with our previous observation that higher levels of copy number change are associated with increased likelihood of recurrence after DCIS (18), but considerably larger cohorts of DCIS are required to test this hypothesis, especially given the multiple interacting variables that will need to be considered (ER status, HER2 status, grade, therapy type, etc.). The utility of a biomarker panel combining tumor-intrinsic copy number data in combination with tumor-extrinsic immune markers remains to be investigated.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: S. Hendry, K.L. Gorringe, S.B. Fox
Development of methodology: S. Hendry
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S. Hendry, J.-M.B. Pang, D.J. Byrne, M.C. Cummings, G.B. Mann, S.B. Fox
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S. Hendry, K.L. Gorringe, S.B. Fox
Writing, review, and/or revision of the manuscript: S. Hendry, D.I. Byrne, S.R. Lakhani, M.C. Cummings, I.G. Campbell, G.B. Mann, K.L. Gorringe, S.B. Fox
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S. Hendry, D.I. Byrne, S.R. Lakhani, M.C. Cummings
Study supervision: I.G. Campbell, K.L. Gorringe, S.B. Fox

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